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THE SURGICAL TREATMENT OF SPASMODIC TORTICOLLIS

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THE involuntary, uncomfortable, and irregular jerking movements of the head which characterize spasmodic torticollis impose a physical and mental burden upon the patient. They interfere with and sometimes prevent the proper performance of occupational duties and enjoyment of social activities. The disorder has been recognized for centuries and has failed to respond to many forms of treatment. However, modern neurosurgical technics have brought many successful results.

Spasmodic torticollis has been adequately defined by Patterson and Little[1] as "an involuntary hyperkinesis manifesting itself by mobile, tonic, or clonic spasms of the neck musculature, and producing more or less stereotyped deviation of the head into an abnormal position, the chin being rotated to one side or the head bent directly forward (antecollis) or backward (retrocollis)." The spasms are abolished by sleep and aggravated by emotional stress, but the cause of the disorder is not known. Although a pure psychogenic origin is upheld by a few neurologists, such a cause is extremely rare, and most modern writers favor the theory of organic origin. This condition must be differentiated from the ischemic or traumatic wry-neck of childhood due to injury to the sternomastoid muscle; in the latter there is a constant contraction due to shortening of the muscle as a result of infiltration of the intramuscular fasciae, as pointed out by Rugh,[2] while the muscle contractions of spasmodic torticollis are irregular and clonic in nature. It is also obviously different from the constant moderate head tilt observed in ocular torticollis, caused by disorders of the eye muscles, as described by Kennedy.[3]

Although many patients with spasmodic torticollis appear to have an unstable nervous make-up, it is extremely difficult for a careful observer to attribute the violent and uncontrollable neck spasms which occur to "nervousness," hysteria, psychoneurosis, or other psychologic disorders. It seems much more likely that the condition is related to the dystonias and athetoses, in which definite organic changes have been found in the basal ganglia of the brain.

Opportunities for careful studies of the brain in spasmodic torticollis are rare, as the disease does not cause death. In 1 man who died at the age of 90, having had spasmodic torticollis for forty-seven years, Alpers and Drayer[4] reported that postmortem examination of the brain revealed atrophy of the neostriatum, marked disease of the large ganglion cells of the putamen and caudate nucleus, less severe involvement of the small ganglion cells, and moderate disease of the pallidal ganglion cells. The cortex and the other basal ganglia were normal. These authors cited 4 other cases with necropsy studies in which neostriatal changes were found. They concluded that in some cases of spasmodic torticollis there is an organic basis. A cause for such changes in

the basal ganglia is not clear from analysis of the histories of most patients with spasmodic torticollis.

It has been thought by some that encephalitis might play an important role in etiology, but Patterson and Little[1] in a survey of 103 patients found a definite history of previous inflammation of the brain in only 5 cases. It was their impression that the extrapyramidal and vestibular systems are involved in the mediation of most cases of spasmodic torticollis and that psychogenic causation is rare. Trauma of the brain or of the cervical region of the spine does not appear to be of etiologic importance. In spite of an apparent organic basis for most cases, occasional reports of relief by psychotherapy, such as those of Rand[5] and others, cannot be overlooked. Repeated rotational movements of the head over a prolonged period of time, as required in certain occupations, have been thought by some to play a part in the initiation of spasmodic torticollis.

The chief clinical manifestation of the condition is a series of irregular jerky movements of the head, the chin being turned toward one side and tilted upward. If the head is turned toward the left, the right sternomastoid muscle appears to be hypertrophied and to contract irregularly, and if turned toward the right, the left sternomastoid muscle appears to be affected. These movements may begin gradually at any time of life, becoming more severe with the passing of years, occurring throughout the patient's waking hours, and in abeyance only during sleep. The violent muscular contractions are most uncomfortable and may be painful. In addition to the evident spasm of the sternomastoid, all of the other superficial and deep rotator muscles of the neck are involved; The importance of the latter was not appreciated for many years. These include the smaller muscles such as the several rectus capitis and obliquus capitis muscles with attachments to the atlas, axis, and occipital bone, as well as the larger muscles such as the trapezius, splenius capitis, longissimus capitis, semispinalis capitis, longus capitis, levator scapulae, and scaleni. The patient is unable to control these movements voluntarily or to prevent them except, strangely enough, by slight pressure against the chin, a phenomenon which supported Brissaud's[6] idea of a psychogenic origin.

In addition to psychotherapy, various nonsurgical measures have been tried for the relief of this condition. Physical therapy, including heat, massage, manipulation, head traction, and electricity, have failed, and sedatives, braces, and collars have proved of little or no avail. Rugh[2] has reported relief by prolonged fixation of the head, neck, and shoulders in plaster for periods of six months to two and a half years.

Prior to 1891 surgical efforts to relieve the condition were limited chiefly to sections, resection, or tenotomies of the sternomastoid muscle, although Campbell de Morgan[7] (1866) was among the first to resect the spinal accessory nerve in the neck, thus paralyzing the muscle. Nerve stretching was also tried. None of these procedures gave satisfactory results. It finally became apparent that the nerve supply to the other rotator muscles of the neck must also be interrupted. In 1891 Keen[8] reported unilateral section of the posterior divisions of the first three cervical nerves at their exits from the intervertebral foramina.

Later surgical experiences brought about important technical changes which gradually led to the modern operation.

Taylor[9] (1915) reported the first intraspinal attack upon this condition, carrying out unilateral division of the sensory roots of the upper four cervical nerves, following a suggestion by Foerster[10] for reduction of incoming stimuli from the muscles in the relief of the spasticity of Little's disease; in this case he also divided the spinal accessory nerve in the neck. McKenzie[11] (1924) reported an operation in which Cushing performed an intrameningeal section of the spinal accessory nerve at the jugular foramen and of the motor and sensory roots of the upper three cervical nerves on the same side. Finney and Hughson[12] (1925) divided both spinal accessory nerves in the neck and performed a bilateral section of the posterior divisions of the upper three cervical nerves at their points of emergence from the intervertebral foramina.

Dandy[13] reported 8 cases in which he had performed intradural section of the anterior and posterior roots of the upper three cervical nerves on both sides and bilateral section of the spinal accessory nerves in the neck. Of these patients 5 were practically cured, 2 were greatly improved, and 1 died of pneumonia three weeks after operation. In later cases he performed the same operation but preserved the posterior roots, and the results were equally satisfactory. Since that time the latter operation has been employed by most neurosurgeons for the relief of intractable spasmodic torticollis. Adson, Young, and Ghormley[14] (1946) found that this procedure sometimes resulted in subluxation and anterior curvature of the upper cervical vertebrae with falling forward of the patient's head and interference with swallowing, breathing, and speaking. In order to prevent this sequel they recommended the use of a bone graft from the ilium extending from the occipital bone to the level of the fifth cervical lamina on both sides. This was carried out immediately after the completion of the nerve sections, and the head and neck fixed in plaster for ten to twelve weeks.

In 1947 Putnam and Herz[15] reported successful results with intradural section of the first three cervical anterior nerve roots on both sides and of the spinal accessory nerve in the neck. In the event that such an operation should give inadequate relief they recommended additional section of the posterior divisions of the fourth cervical to the seventh cervical nerves in the neck. In those cases in which the dystonia involved the muscles of the back or arms they suggested that anterior cordotomy might improve the condition.

Unsatisfactory experiences with conservative measures in the treatment of spasmodic torticollis at the Cleveland Clinic have led to the adoption of intradural section of the anterior cervical nerve roots and section of the spinal accessory nerve in the neck as the operation of choice. With the patient in the upright position under general anesthesia, a complete laminectomy of the first two cervical vertebrae is performed, and the anterior roots of the first three cervical nerves on both sides are divided between silver clips. In order to obtain adequate exposure of the third cervical nerve roots, it is advisable to remove also a portion of the upper margin of the lamina of the third cervical vertebra. Section of the posterior sensory nerve roots is not necessary. The

fourth cervical nerve roots must be left intact in order to avoid possible difficulty in swallowing and respiration. In our experience it has not been necessary to fix the head and neck in plaster after this procedure. About one week after the rhizotomy, an incision is made along the anterior border of the sternomastoid muscle which has been in spasm, and the spinal accessory nerve is identified as it enters the muscle and is resected and ligated. The latter procedure may be carried out first if so desired, but in the writer's experience section of the spinal accessory nerve alone has not given satisfactory relief, and it has always been necessary to divide the first three cervical anterior nerve roots as well. In one instance (case 5) rhizotomy alone succeeded in giving complete relief, and spinal accessory nerve section was not necessary. In the other cases the combined operation was required for adequate relief. In no case was section of both spinal accessory nerves required.

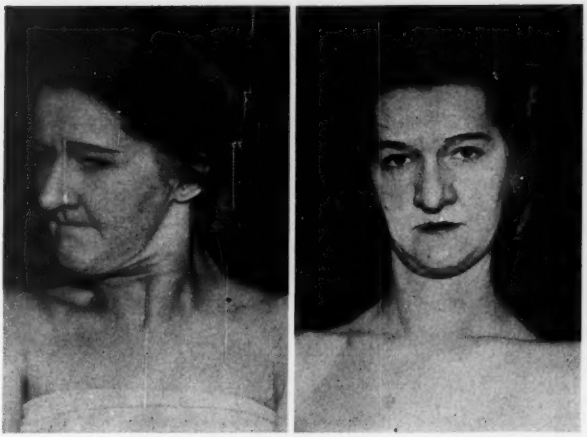
Case Reports

The following brief case reports illustrate indications for operation and the results obtained.

Case 1. A woman, aged 27, complained that five months previously her head had jerked slightly to the left several times within an hour. Three months later "something gave" in the back of the neck, and her head turned to the left and remained there. She tried head traction, chiropractic treatments, diathermy, massage, triple bromides, and benzedrine, without relief. Intradural section of the upper three cervical anterior nerve roots was performed on November 12, 1937, and the right spinal accessory nerve in the neck was divided two weeks later. Since then there has been no more spasm of the neck muscles, and the patient has been able to do her housework and care for her child. The motions of her head are quite limited, and there is some asymmetry of the neck due to the unilateral atrophy of the right sternomastoid and trapezius muscles. When last seen on November 21, 1946, she was nervous but in good general health and working steadily.

Case 2. A man, a clerk, aged 42, for twenty-three years had noticed a tired aching sensation in the back of the neck which was gradually increasing. Four years prior to admission his head had begun to turn to the left involuntarily and had developed irregular jerking movements in that direction. Chiropractic and osteopathic treatments, physical therapy, and saline injections failed to give relief. Examination showed spasmodic contractions of the right sternomastoid muscle with the head rotated to the left and the chin elevated. Bilateral section of the first three cervical anterior nerve roots was performed on October 14, 1938, and ten days later the right spinal accessory nerve was divided in the neck. Since then there has been no more jerking of the head, but the patient has continued to have a very fine tremor of the head and hands. In 1945 the left spinal accessory nerve was divided in the neck at another clinic in an effort to relieve the fine tremor of the head and hands. When last seen at the Cleveland Clinic on November 25, 1947, the patient was well and working, without his former violent head movements, but still exhibiting a fine tremor of the head and of the right hand.

Case 3. (Fig. 1) A woman, aged 39, complained that eighteen years previously while operating a comptometer her head had begun to turn involuntarily to the right. This condition had become worse and uncontrollable through the years. The patient was very nervous. Examination showed spasmodic contractions of the left sternomastoid, and the head was turned to the right. Bilateral anterior rhizotomy of the first three cervical nerves was carried out on April 29, 1940, and the left spinal accessory nerve in the neck was divided on May 8, 1940. She had no more violent jerking movements of the head after operation, but she continued to be generally nervous and when last seen at the Clinic on January 7, 1948,



a *b*

FIG. 1. Case 3. Spasmodic torticollis. (a) Before operation. (b) After operation.

still exhibited a slight head tremor and atrophy of the left sternomastoid and trapezius. She was working steadily.

Case 4. A man, a cook and meat-cutter, aged 52, eight months previously had noticed a burning sensation over the lower part of the right sternomastoid. Soon thereafter his head began to jerk spasmodically to the right, and the neck "cracked" and ached. The condition became steadily worse and failed to respond to manipulation, heat, massage, or medicine. Examination showed a nervous man with spasmodic jerking of the head to the right. There was also some apparent involvement of the muscles of expression in the face. Sedatives, heat, and massage had failed to produce relief. On November 16, 1945, the left spinal accessory nerve was divided, and one week later bilateral section of the anterior roots of the first three cervical nerves was carried out. One year later the patient was reported to be well and having no jerking of the head. He was steadily employed and able to enjoy fishing and hunting.

Case 5. (Fig. 2) A recently discharged soldier, aged 26, had noted a gradually progressive contraction of the neck muscles with turning of the head to the left side over a period of six months. He was able to replace his head in normal position with his hand, and while lying down or standing with his head against a wall he could control its movement in any direction. The disorder prevented him from working. A neck brace, psychiatric treatment, medication, chiropractic and osteopathic manipulations had not given relief. Examination showed the head tilted and turned to the left without spasm of the sternomastoids. Bilateral anterior rhizotomy of the first three cervical nerves was performed on December 5, 1946, producing complete relief so that it was not necessary to divide the spinal accessory nerve. When last seen ten months later the patient was comfortable, free from head tilt or neck spasm, and working steadily. There was a good range of motion in the neck.

In none of the cases discussed was there any obtainable history of severe injury to the head or neck, encephalitis, meningitis, or any specific emotional upset. The first 4 patients might be termed "high-strung" or "nervous." Roentgenologic examination of the cervical region of the spine in each patient failed to reveal any significant abnormal changes in the bones or joints which might help to explain the origin of the condition. The occupation of 1 patient

a *b*

FIG. 2. Case 5. Spasmodic torticollis. (a) Before operation. (b) After operation.

(case 3), a comptometer operator, might be considered of some etiologic importance, inasmuch as her work required frequently repeated rotation of the head for several years. It is conceivable that a habit pattern might have been established by such motion.

By means of the operation described, satisfactory results have been obtained. Immobilization in plaster after operation or fixation with bone graft have not been found necessary (probably due to the fact that only one spinal accessory nerve is divided). The period of hospitalization is approximately three weeks. Untoward complications have yet to be encountered, and each of these patients has been able to return to useful work.

A certain asymmetry in the appearance of the head and neck is unavoidable because of unilateral atrophy of the sternomastoid and trapezius muscles as a result of section of one spinal accessory nerve. A fine tremor of the head may persist in some cases after operation, and there is usually some limitation of rotation of the head toward the side opposite that of the divided spinal accessory nerve. In spite of these minor sequelae, the morale and economic usefulness of the patient are greatly improved by relief from the former violent spasmodic jerking movements of the head.

References

1. Patterson, R. M., and Little, S. C.: Spasmodic torticollis. J. Nerv. and Ment. Dis. **98**:571-599 (Dec.) 1943.
2. Rugh, J. T.: Spasmodic torticollis; its cause and treatment. Am. J. Surg. **49**:490-495 (Sept.) 1940.
3. Kennedy, R. J.: Ocular torticollis. Cleveland Clin. Quart. **13**:163-165 (July) 1946.
4. Alpers, B. J., and Drayer, C. S.: Organic background of some cases of spasmodic torticollis. Report of case with autopsy. Am. J. M. Sc. **193**:378-384 (March) 1937.

5. Rand, C. W.: The Neurosurgical Patient: His Problems of Diagnosis and Care (Springfield: Charles C Thomas, 1944) p. 500.
6. Brissaud, E.: Lecons sur les Maladies Nerveuses (Paris: G. Masson, 1895) pp. 512-520.
7. De Morgan, C.: Case of excision of a part of the spinal accessory nerve for spasmodic wry neck. Brit. and For. M.-Chir. Rev. **38**:218 (July) 1866.
8. Keen, W. W.: A new operation for spasmodic wry neck: namely, division or exsection of the nerves supplying the posterior rotator muscles of the head. Ann. Surg. **13**:44, 1891.
9. Taylor, A. S.: Operations on the peripheral and cranial nerves. In Unilateral Laminectomy in Operative Therapeusis, edited by Johnson, A. B. (New York: D. Appleton and Company, 1915) p. 525.
10. Foerster, O.: On indications and results of excision of posterior spinal nerve roots in man. Surg., Gynec. and Obst. **16**:463-474, 1913.
11. McKenzie, K. G.: Intrameningeal division of the spinal accessory and roots of the upper cervical nerves for the treatment of spasmodic torticollis. Surg., Gynec. and Obst. **39**:5-10 (July) 1924.
12. Finney, J. M. T., and Hughson, W., Spasmodic torticollis. Ann. Surg. **81**:255-269 (Jan.) 1925.
13. Dandy, W. E.: Operation for treatment of spasmodic torticollis. Arch. Surg. **20**:1021-1032 (June) 1930.
14. Adson, A. W., Young, H. H., and Ghormley, R. K.: Spasmodic torticollis; severe organic type treated by combined operation, rhizotomy and fusion. J. Bone and Joint Surg. **28**:299-308 (April) 1946.
15. Putnam, T. J.; and Herz, E.: Treatment of spasmodic torticollis, report of 2 cases. Arch. Neurol. and Psychiat. **57**:260 (Feb.) 1947.

POLYCYTHEMIA VERA RUBRA TREATED WITH NITROGEN MUSTARD

Report of a Case

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IT has been suggested by Jacobson *et al.*[1] that polycythemia may be controlled by nitrogen mustard. These workers observed 5 cases, the longest remission extending over seventeen months.

The case of polycythemia vera rubra reported here was adequately managed with the methyl bis-amine form of nitrogen mustard. The results support the view of Jacobson and his colleagues.

Case Report

A man, aged 51, came to the Cleveland Clinic complaining of progressive exhaustion and nervousness. Four years previously, while working as a gasoline station attendant, he had noted impaired vision and inability to coordinate his hand movements properly. A diagnosis of polycythemia was made, and he was given 12 to 15 x-ray treatments, which apparently resulted in some improvement. On admission his blood pressure was 212 systolic, 130 diastolic. The conjunctivae were injected and the patient appeared plethoric. The spleen was palpable 2 fingers' breadth below the left costal margin. The fundi revealed findings consistent with essential hypertension and grade II arteriosclerosis. Clubbing of the fingers was not noted. The urinalysis, blood sugar and urea, and Wassermann and Kahn reactions were normal. The urea clearance was 60 per cent the first hour and 62 per cent the second hour. Roentgenologic examination of the chest and an electrocardiogram did not reveal any abnormal findings. The complete blood count was 8,640,000 red cells; hematocrit reading 76 cc., or 169 per cent of normal; volume index 0.98; hemoglobin 162 per cent; white blood count 13,500; neutrophils 79 per cent; lymphocytes 13 per cent; eosinophils 5 per cent; monocytes 3 per cent. The total blood volume determination by means of the congo red test was 98 cc. of cells per kg. body weight.

The patient was given nitrogen mustard intravenously, 0.1 mg. per kg. body weight daily on four consecutive days. One month later the blood count was 7,330,000 red cells; hematocrit reading 133 per cent; hemoglobin 136 per cent; white blood count 5500; and the total blood volume 59 cc. of cells per kg. of body weight. The exhaustion and the nervousness were subsiding, the plethora and conjunctival congestion had improved, and the spleen was no longer palpable. Additional treatment was not instituted.

Approximately six months following the patient's initial visit, the red blood count was 6,030,000; hematocrit reading 134 per cent; hemoglobin 124 per cent; white blood count 10,950; neutrophils 82 per cent; lymphocytes 12 per cent; eosinophils 5 per cent; monocytes 1 per cent, and the total red cell mass was 39 cc. per kg. body weight. The nervousness was gone, the exhaustion was almost absent, and the plethora and conjunctival congestion were absent. Splenomegaly remained absent.

Comment

A case of polycythemia vera rubra is being successfully controlled by the methyl bis-amine form of nitrogen mustard. Though adequate control is being maintained approximately six months following treatment, sufficient time has not elapsed for a complete evaluation of nitrogen mustard as a therapeutic agent in this disease.

Reference

1. Jacobson, L. O., *et al.:* Nitrogen mustard therapy; studies on effect of methyl-bis (beta-chloroethyl) amine hydrochloride on neoplastic diseases and allied disorders of hemopoietic system. J.A.M.A. **132**: 263-271 (Oct. 5) 1946.

UNUNITED FRACTURES OF THE NECK OF THE FEMUR

Modern Concepts of Treatment

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THERE is a widespread assumption on the part of the general public and many medical men that, with the use of internal fixation, the problem of treatment of fractures of the neck of the femur has been completely and successfully solved. This method of management has marked an important milestone, but it has not provided the complete and final solution in such fractures. Before internal nailing was used, union occurred in only about 50 per cent of intracapsular fractures of the femur, whereas now about 80 per cent of such fractures unite. However, appraisal of results merely from the standpoint of bone healing does not tell the whole story. When the results are considered from the standpoint of function they are unsatisfactory in a rather large proportion of cases in which union is obtained. The group in which atrophic changes in the head and arthritic complications result even though union occurs, added to the approximately 20 per cent of cases in which the fracture fails to unite, comprises about 35 to 50 per cent of all fractures of the femoral neck. Thus treatment with internal fixation may be said to be actually successful in only one-half to two-thirds of such cases. These figures indicate that there is room for considerable improvement in the treatment of this type of fracture.

Until very recently it has been generally thought that the outcome of treatment of a fracture at the neck of the femur depended solely on the degree of interruption of the blood supply, and this was regarded as an unpredictable and uncontrollable factor. It was thought that all that could be done was to nail the fragments together and to hope that the circulation remained sufficiently intact to furnish nutrition for bone healing and to prevent aseptic necrosis of the head. Even when there has been convincing roentgenographic evidence of nonunion, the tendency has been to hang on to the blind hope that the efficiency of the circulation would somehow be restored and that the fracture eventually would heal. This hoped-for eventuality almost never happened. The result has been that patients with nonunion following an intracapsular fracture of the femur have been incapacitated for years while avascular changes were progressing to aseptic necrosis and eventual collapse of the head fragment, and they and their surgeons were hoping for the impossible. Finally, when a secondary operation was recognized as imperative, the long delay had often so complicated the situation that a formidable and extensive reconstruction procedure, which could never yield entirely satisfactory results, was required.

In elderly persons, in whom the majority of hip fractures occur, the auxiliary circulation through the ligamentum teres is minimal or lacking. Hence

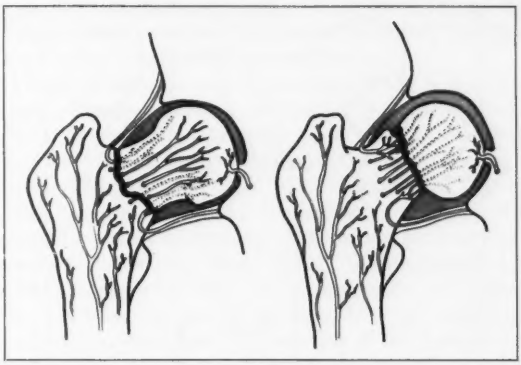

FIG. 1. Circulation to head and neck of femur, indicating relationship of position of fracture to interruption of blood supply.

circulation to the head of the bone is maintained almost entirely by the capsular vessels that enter the base and posterior part of the neck of the femur and extend upward through the medullary vessels. When a fracture of the neck of the femur occurs there is a definite interruption of this blood supply to the head. The degree of circulatory impairment varies with the position of the fracture (fig. 1). When the fracture is near the base some blood supply remains in the head fragment, but in subcapital fractures the head segment is almost devoid of circulation. In the treatment of fractures of the neck of the femur, the earlier this main source of blood supply can be restored through the neck by impaction of the fracture and stimulation of osteogenesis and revascularization, the better the results should be.

Recent studies of cases in which a fracture at the neck of the femur has failed to unite or in which treatment has been unsatisfactory from the functional standpoint have confirmed the fact that the reestablishment of the circulation is of prime importance in determining the outcome of treatment. Whether or not nonunion or aseptic necrosis or both occur depends on the degree of interruption of the blood supply, especially to the amputated head fragment. These studies have shown further that the reestablishment of the circulation is closely related to and partially dependent on a mechanical factor, that is, the shearing strain on the fractured surfaces.

The mechanical factor has been investigated in detail by Pauwels,[1] Linton,[2] and Eyre-Brook and Pridie.[3] They all have found that in fractures at the neck of the femur which have failed to unite, the angle of the fracture tends toward the vertical (when measured in relation to the femoral shaft), the fracture is not impacting, and shearing force tends to pull the fractured surfaces apart, even when they are satisfactorily nailed. These authors all use different methods for measuring the inclination of the fracture plane, but all are estimating the same factor, the degree of shearing strain tending to pull the fragments apart

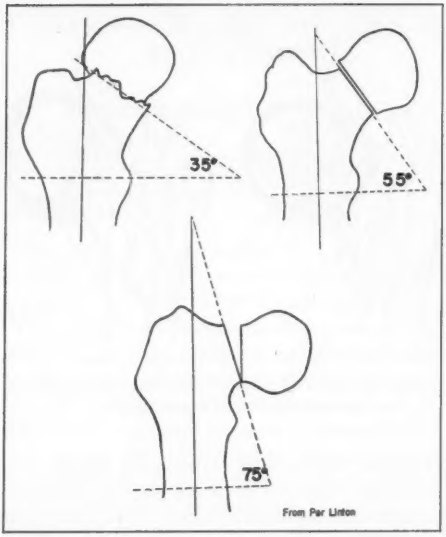

FIG. 2. Mechanical analysis of fractures at neck of femur, according to Linton.

and to prevent bony union and reestablishment of circulation and revascularization. They all agree also that in fractures in which the unfavorable shearing stress is greatest, the incidence of nonunion and other complications is highest. Conversely, when the angle of the fracture is such that the fragments are in an impacting position, treatment usually is satisfactory and complications rarely occur.

To appraise this mechanical factor in the individual case I prefer Linton's method of measuring the angle (fig. 2), since it is simpler than the others and is not affected by adduction or abduction of the leg. The roentgenogram is made with the leg in internal rotation, and the angle measured in relation to the femoral shaft. Linton classifies intracapsular fractures into three groups according to the angle between the line of fracture and the perpendicular to the long axis of the femur. If this angle is less than 35 degrees the fracture is in an impacting position, there is no shearing stress, and it will unite soundly with any type of treatment (group I). It is probably in fractures of this type that the majority of instances of successful healing occurred before the advent of internal nailing. If the angle is between 35 and 60 degrees, there is less impaction and some shearing strain. Fractures of this type (group II) probably will not unite unless this shearing force is overcome by internal fixation. It is probably this group that accounts for most of the additional 30 per cent of cases of femoral neck fractures in which healing occurs since the method of internal fixation was introduced. When the angle of the fracture plane is 60 to 80 degrees, the fracture line is so nearly vertical and the effect of shearing

stress is so great that nonunion or other complications may be anticipated (group III), regardless of whether a Smith-Petersen nail, multiple pins, or the lag screw is used as the method of internal fixation.

Since the principal blood supply to the head of the femur is by way of the medullary vessels which pass through the neck (fig. 1), it is obvious that when the fracture is in an impacting position there will be relatively prompt reestablishment of the blood supply to the head, that bone healing will progress, and that atrophic changes in the head will be prevented. Conversely, it is to be expected that when shearing strain causes pulling apart of the fractured surfaces, reestablishment of circulation through the neck of the femur is delayed or prevented. When the blood supply is thus impaired, fibrotic and atrophic changes ensue, with eventual degeneration and necrosis of bone. Whether or not this bony change occurs depends on the degree of interruption of the blood supply, as determined by the angle of the fracture and its position within the capsule. This demonstrates the importance of the mechanical factor in relation to the circulatory factor in intracapsular fractures of the femur. When shearing force makes impaction impossible and circulation of the head fragment is greatly impaired, union is delayed or prevented. If the process of healing is too slow, it seems reasonable to assume that serious atrophic changes may develop in the head, even though bony union eventually takes place.

The recognition of the fundamental importance and correlation of the mechanical and circulatory factors in intracapsular fractures of the neck of the femur makes possible a reorientation of our conceptions and the formulation of principles leading to modifications in the method of treatment of ununited fractures.

Treatment of Ununited Fractures of Neck of Femur

In the treatment of ununited fractures in other parts of the skeletal system, it has long been recognized that satisfactory results depend on the correction of faulty mechanics and stimulation of osteosynthesis by bone grafting as soon as possible after evidence of nonunion appears. However, in treating ununited fractures of the neck of the femur, when evidence of nonunion appeared, we have tended to wait for months, and even years, in the vain hope that union might eventually occur. This almost never happened, and then, even when secondary intervention was resorted to, we have not made use of the principles of combined surgical treatment that have proved successful in other parts of the body. Instead we have relied either on bone grafting and failed to take into account the mechanical factor largely responsible for the nonunion or on osteotomy, attempting to place the fracture in an impacting position, doing nothing to replace the fibrous tissue which had formed at the fracture site and thus facilitate osteogenesis and revascularization of the head.[4]

Both bone grafting and osteotomy, by themselves, are only partial procedures, in that each fails to consider the problem as a whole. Figure 3, showing the principal bone grafting procedures that have been recommended, and fig. 4, showing the usual types of osteotomy operations, clearly exhibit the disadvantages of each when used separately. One of the principal difficulties encountered with the various osteotomy procedures has been the lack of definite

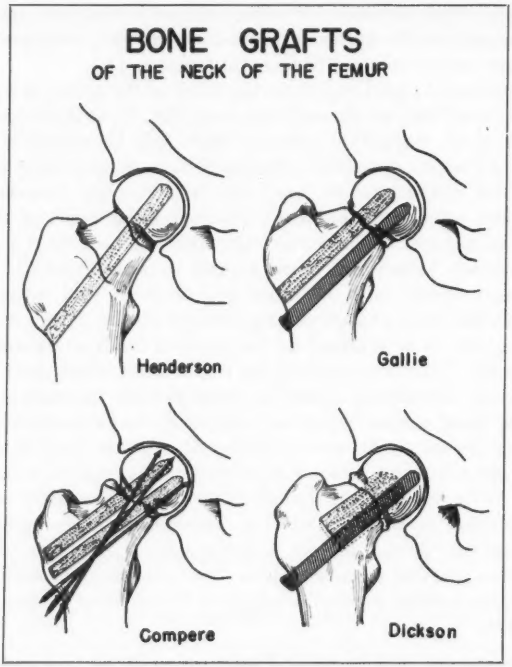

FIG. 3. Various types of bone-grafting procedures used for ununited fracture of the neck of femur.

control over the head of the femur and the upper trochanteric segment and their proper placement when the shaft of the femur is displaced medially. In many instances the head of the femur is not rotated sufficiently and the fragments are not correctly placed to facilitate bony union and repair. Both bone grafting and osteotomy have produced satisfactory results in a certain proportion of cases, and the individual surgeon, on the basis of his own experience, has tended to develop a preference for one or the other. This empirical attitude has undoubtedly been responsible for many failures by both methods, since it has failed to recognize that a certain proportion of cases in which bone grafts are used will result in failure when shearing force on the fracture line remains great, and also that an osteotomy will not be successful when the desired impaction is not obtained because of lack of accurate control of the rotation of the head or when the degenerative fibrous process at the fracture site has progressed so that circulation cannot be reestablished through the neck to stimulate osseous repair.

A critical analysis of my own results with various technics, of both bone grafting and osteotomy, and a review of the literature concerned with various

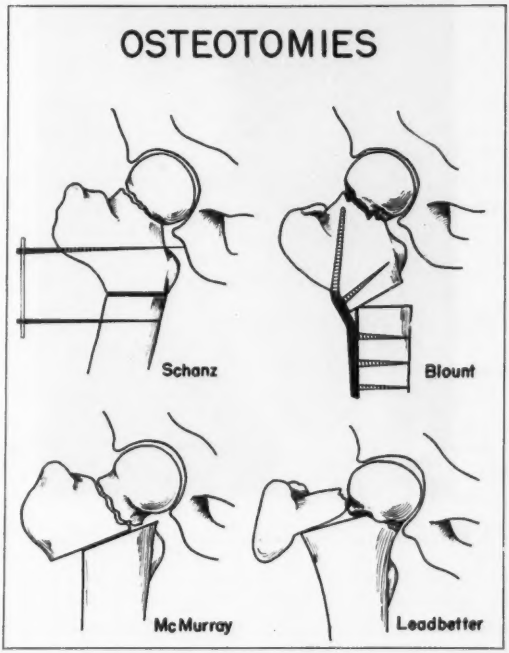

FIG. 4. Various types of osteotomies used for ununited fracture of neck of femur.

methods,[2] demonstrated that the proportion of failures of operations on ununited fractures of the femoral neck is remarkably similar with all methods, amounting quite generally to 35 to 50 per cent of all cases subjected to secondary procedures. This analysis, together with a study of the basic mechanical and circulatory factors, led to the idea that if the advantages of the various procedures could be combined, with the aim of correcting faulty mechanics and of restoring circulation and stimulating bone formation, in a single operation, perhaps these results might be improved.

Examination of a series of roentgenograms of ununited fractures of the femoral neck showed that in most instances there was a downward rotation of the head of about 60 degrees (figs. 5 and 6). Furthermore, measurement of the angle of the fracture line in relation to the femoral shaft by Linton's method showed that in all instances this was high, that is, over 65 degrees.

After full consideration of all the foregoing data it seemed evident that, in order to rotate the head to its normal anatomic relationship within the acetabulum, to overcome mechanical stress, and to assure impaction of the fractured surfaces, a rotation of 60 degrees of the upper part of the shaft and head of the femur should be accurately and consistently obtained. The fracture would then always be in group I, according to Linton's classification, and

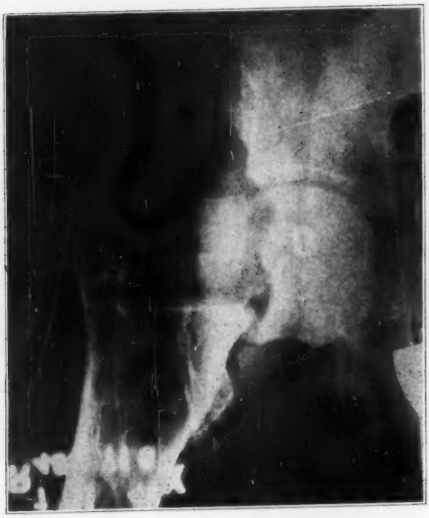

FIG. 5. Roentgenogram of typical ununited fracture of femoral neck.

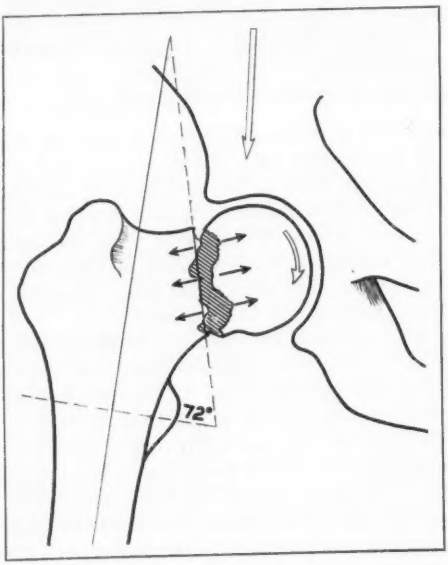

FIG. 6. Mechanical analysis of fracture shown in fig. 5.

satisfactory healing should occur. Since bone grafting stimulates osteogenesis, it also seemed logical and desirable that this 60-degree rotation of the head and trochanteric segment should be combined with bone grafting. With this procedure the old scar and fibrous tissue that had formed at the site of the nonunion could be removed and replaced with new cancellous iliac bone. The graft would give added stability across the fracture, would act as a guide to the formation of granulation tissue, and would aid in revascularization of the head. This would facilitate the restoration of circulation from the trochanteric segment to the head and lead to more rapid healing. The bone graft would also aid in preventing overimpaction.

Technic of Operation

A combined procedure was developed to incorporate all these principles. The technic is shown in figs. 7, 8, 9, 10, and 11.

The trochanteric portion and the head of the femur are transfixed with a blade plate or Smith-Petersen nail with blade attached (Jewett nail), penetrating from the lateral prominence of the trochanter into the lower half of the head to assure accurate control of the head and trochanteric segment. In anticipation of a 60-degree rotation, the shaft of the plate should extend outward at an angle of 60 degrees to the long axis of the femur so that proper placement of the plate may be readily accomplished after the osteotomy and necessary rotation are completed (fig. 7).

If the trochanteric section is considered as a regular hexagon (fig. 8) and rotated by one segment, a 60-degree rotation is accomplished. Hence the osteotomy should be made along two sides of what would be a regular hexagon. To obtain the proper position and shape of the osteotomy it was necessary to devise a hemihexagonal marking chisel in which the long diameter equals the distance from the lateral prominence of the trochanter, where the fixation plate or nail entered, to the upper surface of the lesser trochanter (fig. 7, D). By placing this marker on the anterior surface of the femur with one side parallel to the flare of the trochanter as it extends downward from the entrance of the nailplate, the exact site for the osteotomy is determined (fig. 9). If a marker of proper size is used, the lower medial edge of the marker always comes out just above the lesser trochanter, thus assuring a high osteotomy. The upper transfixed fragments are then rotated so that side A is brought into the position of A′ (fig. 9), giving an accurate 60-degree rotation. The plate assumes its proper place along the shaft of the femur, and a stable contact of fragments, with a perfect fit, results (fig. 10).

When the osteotomy and rotation have been completed, a window is made in front of the trochanteric segment just distal to the fracture site (fig. 11). This readily allows removal of sclerotic bone and fibrous tissue and curettement up into the head to facilitate placement of the graft. Numerous chips of cancellous bone are impacted well across the fracture line, and one large graft is then fixed into position to give added stability. The window removed is then replaced. Cancellous bone is used for the graft because it has superior osteogenetic power.

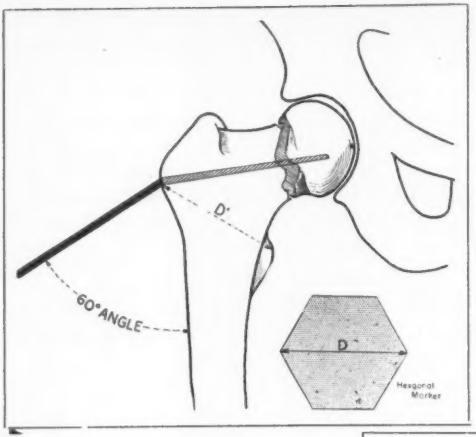

FIG. 7. Transfixion of upper segments with blade at 60 degrees. D' is measured to determine the long diameter of chisel used for marking the site of osteotomy.

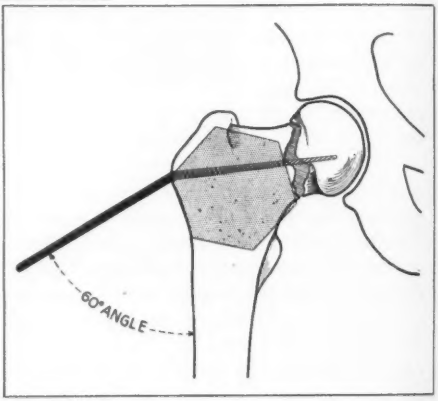

FIG. 8. Placement of hexagonal marker to determine site of osteotomy.

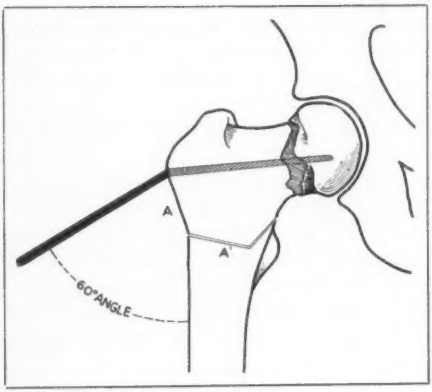

FIG. 9. Site of osteotomy.

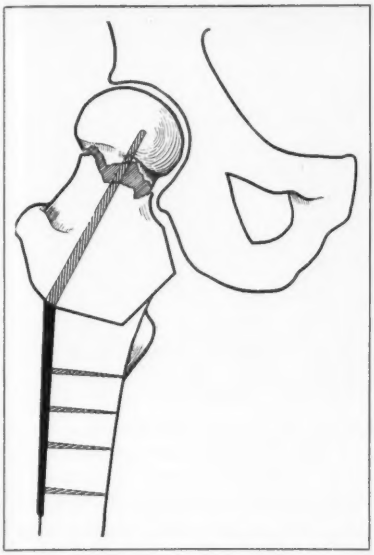

FIG. 10. Rotation of femoral head and trochanteric segment and fixed position of the blade.

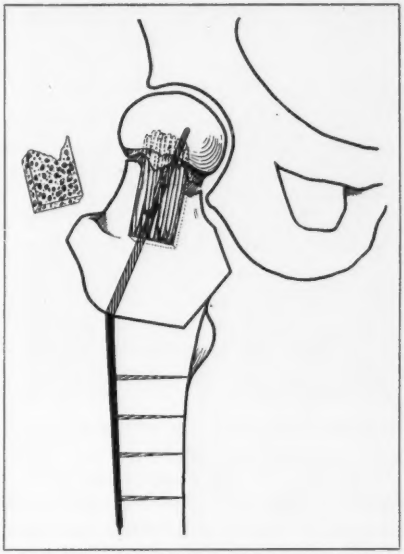

FIG. 11. Window of bone removed to allow curettement of fibrous tissue and placement of bone graft.

A typical case is illustrated in fig. 12. This patient, a man, aged 64, had had a fracture of the neck of the femur ten months previously in which a lag screw had been used for internal fixation; nonunion had resulted.

After the proper preparation and anesthetization (with pentothal and inhalation of nitrous oxide and oxygen), the patient is arranged on the table with the affected hip fixed in internal rotation. It is preferable to have two x-ray units so that both anteroposterior and lateral roentgenograms of the hip can be readily made. This saves much time and facilitates draping of the patient. A preliminary roentgenogram is made so that traction, abduction, and rotation can be adjusted to secure the optimal position.

The region of the fracture is approached by a curved lateral incision between the tensor fascia femoris and the gluteus medius muscles or by an anterior iliofemoral incision. The incision is carried down the outer side of the shaft about 6 or 7 inches to facilitate fixation of the plate. The joint capsule is opened and the incision is carried outward with medial reflection of the muscles on the anterior surface of the femur. This allows adequate exposure with minimum interference with the blood supply.

The Smith-Petersen nail, lag screw, or other type of internal fixation previously used can now be removed readily. The outer surface of the femur is exposed subperiosteally, and a bed is prepared for the reception of the plate after the osteotomy has been completed. A guide pin is then passed from a

point just a little above the prominence of the greater trochanter into the lower half of the head of the femur. This is accomplished with the aid of a special protractor which assures that the pin is placed at a right angle to the long axis of the femur (figs. 13 and 14).

Roentgenograms are made to check the position of the pin and the length of blade that will be required. The blade length varies from 2¼ to 2¾ inches. A proper-sized Jewett nail with an angle of 150 degrees is then threaded over the wire, and the nail is securely fixed as the fractured surfaces are impacted. The plate of the Jewett nail will then extend from the shaft at an angle of 60 degrees. (If there has been little absorption of the neck and the head is riding high in relation to the prominence of the trochanter, it may be advisable to insert the guide wire at 75 degrees to the long axis of the femur and to use a Jewett nail with an angle of 165 degrees.)

The lesser trochanter is palpated, and the distance from the prominence of the greater trochanter, where the blade enters, to the upper surface of the lesser trochanter is calculated with a caliper (fig. 15). A hemihexagonal chisel, with a diameter of this width, is chosen from the set of five chisels with diameters varying in width by ⅛ inch from 1¾ inches to 2¼ inches (fig. 16). The chisel selected is then used to mark the site of the osteotomy. When the proper-sized marking chisel is used and placed vertically on the anterior surface of the femur with the diameter extending from the entrance of the blade to the lesser trochanter, one side of the marker extends beyond the flare of the trochanter (fig. 17). If the chisel is now rotated slightly so that one side runs

FIG. 12. Preoperative roentgenogram showing nonunion.

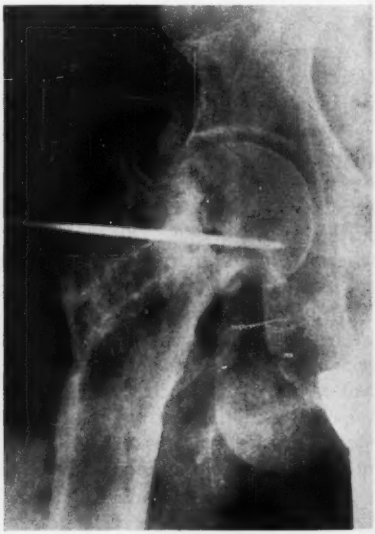

FIG. 13. Roentgenogram showing placement of guide wire.

FIG. 14. Special protractor used to assure a 60-degree projection of plate.

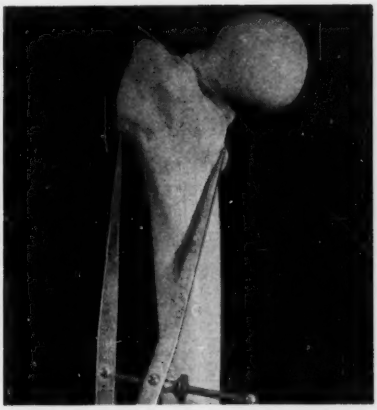

FIG. 15. Method of measuring diameters of special chisels.

parallel to the flare of the trochanter, extending downward from the entrance of the blade, the site of the osteotomy can be marked along the other two blades. This brings the inner blade out just above the lesser trochanter, thus assuring a high osteotomy (fig. 18). If too small a marker is chosen, the osteotomy will extend into the femoral neck (fig. 19) and much of the support of the head segment will be lost. If too large a chisel is used, the osteotomy will come out below the lesser trochanter (fig. 20), and the impacting force of the psoas will not be procured. The measurement determining the choice of the proper marking chisel is extremely important if optimal results are to be obtained from the osteotomy.

The osteotomy is carefully completed with a sharp, thin osteotome. A little traction is applied at this stage, and the osteotomy site is thoroughly mobilized. The shaft of the femur below the osteotomy is then lifted forward so that the upper segment can rotate freely beneath it. Additional traction is applied, and the leg is brought into slight abduction. The two segments are then manipulated slightly forward, and the bone is placed in its new position. The manipulation must be gentle to guard against any fracture of the trochanteric segment. Traction is then released and the blade plate securely fixed to the shaft of the femur (fig. 21).

When the osteotomy and rotation have been completed, a window is made in the anterior surface of the trochanteric segment, just distal to the fracture site. This readily allows removal of sclerotic bone and fibrous tissue and curettement up into the head to facilitate placement of the graft. Numerous chips of cancellous bone from the ilium are impacted well across the fracture line, and one large graft is then fixed into position to give added stability. The removed window is then replaced. Cancellous bone is used because it has superior osteogenetic power.

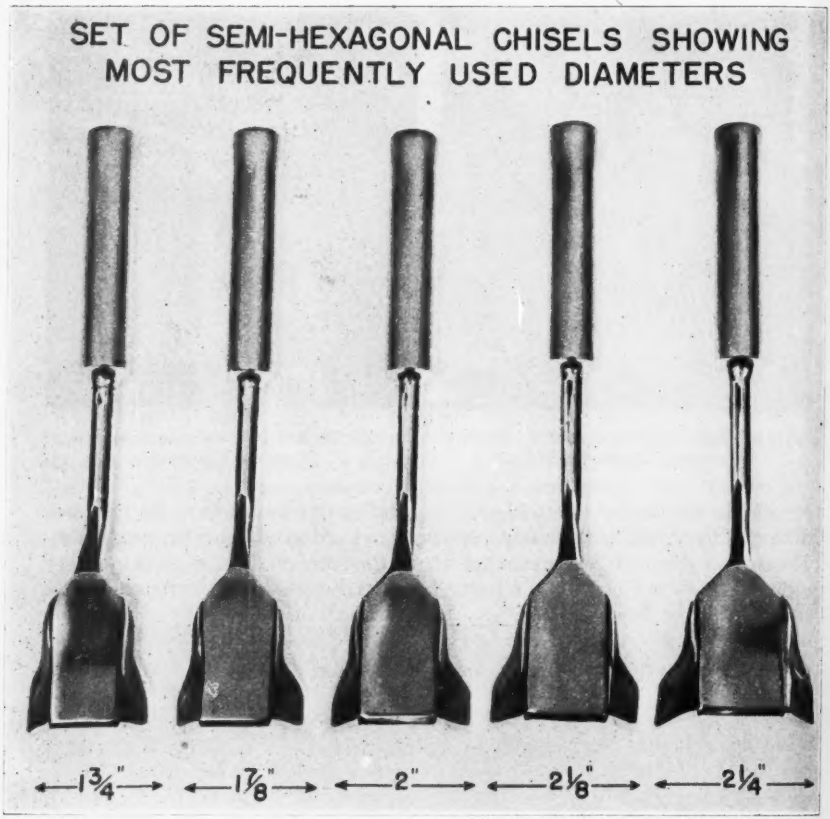

FIG. 16. Set of five hemihexagonal chisels for marking the site of osteotomy.

After operation, internal rotation is maintained in balanced traction or with a plaster boot and bar for six to eight weeks. On the first postoperative day, the prothrombin time is determined and 300 mg. of dicumarol is administered. The prothrombin time of the blood is repeatedly determined, and supplementary doses of dicumarol are given as indicated to keep the prothrombin level at 30 to 50 per cent of normal. This check is continued for a ten-day period. At the end of six weeks the patient is allowed to be out of bed and on crutches. Roentgenograms are made as progress studies from time to time, and protection from weight-bearing is continued until there is evidence that the head is thoroughly revascularized.

Fortunately this type of rotation osteotomy equalizes leg length; the greater the varus deformity before operation, the greater the length procured. In an adult of average size, the increase in leg length after the rotation osteotomy

FIG. 17. Preliminary placement of chisel with correct diameter.

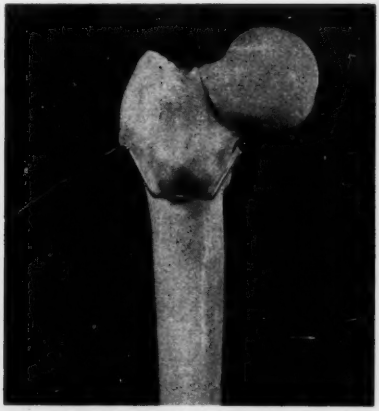

FIG. 18. Placement of chisel to mark osteotomy site.

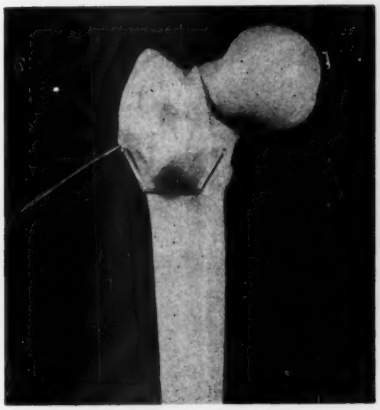

FIG. 19. Effect of using too small a chisel.

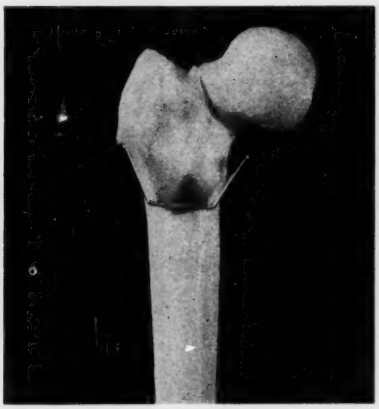

FIG. 20. Effect of using too large a chisel.

amounts to ¾ to 1½ inches (figs. 22 and 23). The elimination of the disadvantage of leg shortening, which has been usual with other types of osteotomy, is a feature of this type of operation that appeals strongly to the patients.

Results

This approach to the treatment of ununited fractures of the neck of the femur has produced most encouraging results, of which the following case is typical. A man, aged 42, had fractured his right hip in July, 1944. Primary treatment consisted of supracondylar traction with a Steinmann pin for three months;

he was then placed in a plaster spica for six months. When he first consulted me a year and nine months after his injury, there was an ununited fracture of the neck of the right femur, with 1½ inches of shortening of the leg (fig. 24). Operation was performed on May 15, 1946, and balanced traction was applied until June 22. He was walking on crutches in July.

The patient's lower extremities were of equal length. Protection with the use of crutches was continued for one year. Full range of motion was procured, and the roentgenogram taken eighteen months after operation (fig. 25) showed excellent union with revascularization of the head of the femur.

In some of the cases dealt with so far the nonunion has been of long standing, and in several, roentgenograms showed increased density in the head

FIG. 21. Roentgenogram showing position obtained by the osteotomy and rotation in case shown in fig. 12.

fragment, indicating a considerable degree of aseptic necrosis. Later there has been roentgenographic evidence of the formation of healthy bone, indicating that circulation to the head has been reestablished through the medullary vessels of the neck as a result of the combined operation.

The restoration of circulation to the head in these cases, and also in some cases reported by others after bone grafting or osteotomy procedures, naturally suggests that perhaps we should question the concepts previously taught regarding necrotic heads after femoral neck fractures. Although no definite dictum can be offered on the basis of present knowledge, it seems desirable at this point to question the practice of sacrificing all so-called dead heads and resorting to reconstructive operations, as some authorities recommend. It

would seem wiser to assume a cautious and conservative attitude toward the removal of dead heads, since according to the facts cited, there is possibility for regeneration of bone in a large proportion of these cases. Nevertheless, we must not lose sight of the fact that although there may be some question as to the degree of vascular damage, there is no question that the nutrition of heads which show increased density on the roentgenogram has been impaired. If the head is not protected during the period while new bone is forming, atrophic and arthritic changes are almost certain to occur.

Plea for Earlier Treatment

Since the combined osteotomy and bone-grafting operation has resulted in evidence of bone regeneration and revascularization in roentgenologically dead heads in cases of two and three years' duration, it seems logical to assume that the treatment might be expedited and the results more certainly favorable in earlier cases of nonunion. When it is recognized that nonunion is developing, this fact should be accepted immediately and an appropriate operation for correction carried out then. Elsewhere in the body, when it is recognized that a fracture is not uniting, bone grafting is resorted to, usually with successful results and much saving of time and disability for the patients. However, when a hip fracture is not uniting, the tendency is to "wait and see" while the condition goes from bad to worse. The longer operation is delayed the greater the degree of atrophic changes in the head and the more problematic the results of secondary treatment. The earlier the operation is performed after nonunion is recognized the better the results should be.

Slipping of the fractured surfaces is usually discerned on the roentgenogram within the first few weeks, and in the vast majority of cases in which this occurs the situation progresses steadily, and there is eventual nonunion. If

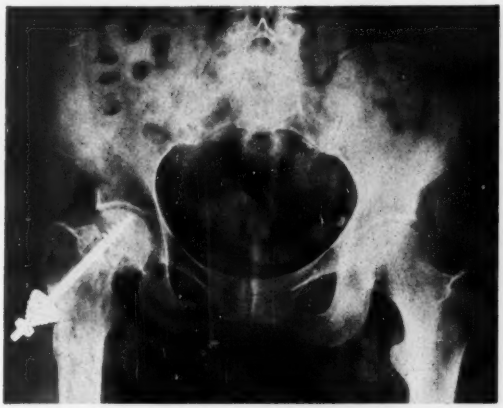

Fig. 22. Roentgenogram showing degree of leg shortening before operation in case shown in fig. 12.

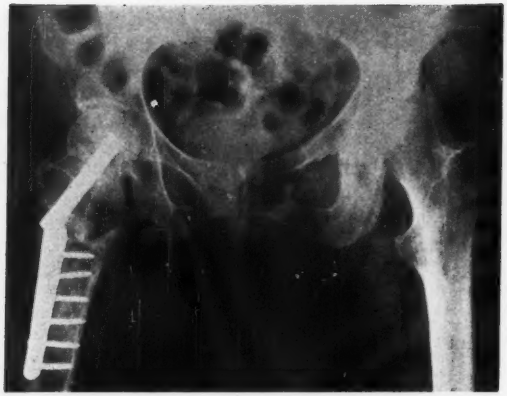

FIG. 23. Roentgenogram showing equalization of leg length after operation in case shown in fig. 12.

FIG. 24. Preoperative anteroposterior roentgenogram, showing nonunion of femoral neck fracture one year and nine months after injury.

FIG. 25. Anteroposterior roentgenogram eighteen months after operation in case shown in fig. 24, showing union and revascularization of the head.

union does finally occur in such cases, it is long delayed and is usually accompanied by severe atrophic changes. In these cases, instead of waiting and hoping blindly for a favorable outcome, which almost never happens, the secondary operation should be performed immediately, assuming that the patient's general condition warrants it. This would establish impaction and revascularization and regeneration of bone before all the troublesome fibrosis and atrophic changes have occurred to complicate the situation. If early recognition and early treatment of nonunion were systematically and generally carried out, the necessity for the more formidable reconstructive operations should be reduced to a minimum.

Several of the illustrations used in this article have been supplied through the courtesy of The Journal of Bone and Joint Surgery. *October, 1947.*

References

1. Pauwels, F.: Der Schenkelhalsbruch ein mechanisches Problem. Grundlagen d. Heilungsvorganges, Prognose und kausale Therapie. (Stuttgart: Ferdinand Enke, 1935.)
2. Linton, P.: On different types of intracapsular fractures of femoral neck; surgical investigation of origin, prognosis and complications in 365 cases. Acta chir. Scandinav. **90**:1-122, 1944.
3. Eyre-Brook, A. L., and Pridie, K. H.: Intracapsular fractures of neck of femur; final results of 75 consecutive cases treated by closed method of pinning. Brit. J. Surg. **29**:115-138 (July) 1941.
4. Dickson, J. A.: High geometric osteotomy. rotation and bone graft, for ununited fractures of neck of femur. J. Bone and Joi . **29**:1005-1018 (Oct.) 1947.

CONTACT X-RAY THERAPY FOR SUPERFICIAL LESIONS

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BIRTHMARKS, keratoses, keloids, warts, local recurrences from cancer of the breast, superficial epitheliomas, and many similar accessible lesions can be quickly and successfully treated with "contact" x-ray apparatus. These conditions also have been treated with caustic chemical agents, surgical procedures with cautery or scalpel, radium, and higher voltage x-rays. During the past eight years contact x-ray therapy has been preferred at the Cleveland Clinic because of several advantages over these methods.

The apparatus (fig. 1) employed was developed by Chaoul in Berlin primarily as a substitute for radium in the treatment of accessible lesions. Its effectiveness depends upon the design of the x-ray tube. The tube is constructed so that the source of the rays (focal spot) is near (2.0 cm.) the opening through which the rays are emitted. Because of this a large quantity of rays is produced (8500 r per minute, no filter), and since the apparatus is operated at low voltage (50 K.V.) the rays have minimal penetrability (20 per cent at 1.0 cm. depth).

The advantages of this method of treatment over others are:

1. The quantity of rays produced is so great that treatment can be given in a few seconds or a minute or two. This is particularly helpful when treating children.

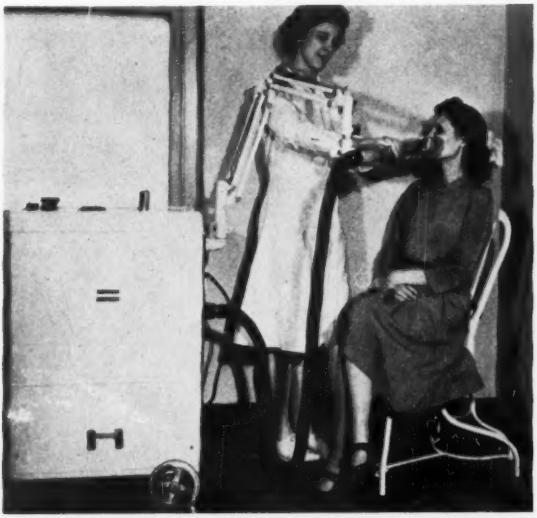


FIG. 1. Contact x-ray apparatus. The apparatus is mobile. The nozzle-like x-ray tube can be fixed on brackets or removed to hold in hands. Cones fit over end of tube.

2. As penetrability of the rays is minimal there is no serious damage to underlying tissues, therefore there is little scar formation. This is particularly beneficial when treating lesions on the face, about the eyes, over cartilages of the nose or ear, and epiphyses, which may be damaged by radium or higher voltage x-rays.

3. The rays can be localized with cones having openings of various sizes and shapes so that tissues adjacent to the lesions are not damaged.

4. Treatment is painless as compared with caustic agents or surgical procedures.

5. This method eliminates the necessity of handling radium, prolonged or careless use of which may cause damage to the radiologist.

6. Treatments can be given at low cost.

Birthmarks

Birthmarks, or hemangiomas, have been classified by dermatologists as nevus flammeus, nevus vasculosus, and angioma cavernosum.

Nevus flammeus, or "portwine" mark (fig. 2), usually occurs on the face and neck but may develop on any part of the body. These nevi vary in color from bluish-red to purple and in size from a few millimeters to 6 or more centimeters in diameter. They are not elevated above the surface of the skin. Some may fade, but most persist. Unlike other vascular nevi, the vessels of which they are composed are mature, consequently they do not respond to irradiation. Small ones in children may respond to irradiation, but those in adults do not, in which case we advise the use of a covering cosmetic.

FIG. 2. Nevus flammeus. Does not respond to treatment.

Nevus vasculosus, or "strawberry mark" (fig. 3), is a red or mottled soft mass of small immature vessels. The nevi are elevated above the level of surrounding skin. They vary in size from a few millimeters to 8 or more centimeters in diameter.

Angioma, or **nevus cavernosum** (fig. 4), is composed of somewhat larger and deeper vessels than nevus vasculosus. These are soft tumors over which the skin may be normal in color or have a bluish tinge from vessels beneath. Nevus vasculosus is frequently present also in the skin over the tumors. The mass of angioma cavernosum is usually only slightly elevated above the level of surrounding skin. These tumors may not be manifest until several months after birth, and they rarely develop after adolescence. They occur most frequently on the cheeks, scalp, chest, and back and occasionally involve the tongue and other mucous membrane areas. Some undergo spontaneous regression, but deep ones may persist.

a *b*

FIG. 3. (a) Nevus vasculosus of cheek and lower lid. (b) Result two years after treatment. No damage to eye or epilation of lid.

Treatment is indicated for both nevus vasculosus and cavernosum because some may not undergo complete involution, traces persisting to adult life. It is also indicated because of the psychologic effect of the unsightly lesions on parents and others.

Gratifying results have been obtained with contact x-ray therapy. There is no necessity for surgical operations. A treatment with contact x-ray can be given in a few seconds, is painless, and there is no damage to underlying or neighboring structures and no subsequent reaction. It is particularly advantageous for angiomas involving eyelids (fig. 5) because the rays usually can be directed away from the eye so that it is seldom necessary to cover the eyeball with lead shields. The anterior chamber of the eye of children is sensitive to irra-

diation, and opacities of the lens may be produced from relatively small quantities, as may result from radium therapy. Also, epiphyses may be damaged by radium or higher voltage x-ray so that bone growth is delayed when such methods are used to treat lesions overlying them. This result is unlikely with contact x-ray therapy because of the low penetrability of the rays and minimal quantity reaching to the depth of the epiphyses.

Treatments may be started when a child is a few months old and are usually given at monthly intervals until improvement or blanching is noticeable. Improvement is generally evident after about four applications, although some cases require a few subsequent treatments every two to four months. We prefer this method of prolonged treatment with relatively small doses, as we formerly used with radium, because there is no danger of ulceration or scar. The usual dose is 300 r with 1.0 mm. A1 filter at 2.1 cm. distance. For deeper

a *b*

FIG. 4. (a) Angioma cavernosa of orbit and upper eyelid. (b) Result three years after treatment. No damage to eye or epilation of lid.

lesions thicker filter (2.5 mm. A1) and greater distance (4.0 cm.) may be necessary.

Senile keratoses and seborrheic keratoses may be single or multiple, gray or brown, flat or slightly raised, horny, crusted lesions developing on exposed skin surfaces or lips, especially in individuals susceptible to actinic rays. Such lesions are dangerous, as they tend to become epitheliomas. Contact x-ray therapy is ideal for treatment. We usually give 2000 to 4000 r unfiltered rays at one treatment, which takes fifteen to thirty seconds. Erythema reaction develops in about eight days, followed by scab formation and healing in about four weeks.

Keloids may develop spontaneously (idiopathic) or in scars (hypertrophy).

a *b*

FIG. 5. Hemangioma of both eyelids and result after one year of contact x-ray therapy without damage to eyes.

Some persons, especially of the colored race, are prone to develop keloids following wounds or on the scars of acne. They are occasionally seen following operations for goiter in patients who do not otherwise develop them. Keloids may be painful. Surgical removal is seldom successful because keloid formation usually recurs. In treatment with contact x-ray, the surrounding skin is protected by lead and the lesions given 300 to 400 r (filter 1.0 mm. Al) at monthly intervals. The number of treatments necessary depends upon the size of the keloid. The cosmetic results are satisfactory, and there is no recurrence. Prophylactic irradiation is indicated following operations on persons with a tendency to develop keloids.

Warts (verruca vulgaris), usually occurring on the hands, and plantar warts (verruca plantar), occurring on the feet, are due to a virus infection. They have been reproduced experimentally by subcutaneous injection of material from the base of warts. Those that appear on the hands yield most satisfactorily to contact x-ray therapy. One treatment of 1500 to 3000 r without filtration at one sitting is usually adequate. Each lesion is individualized and surrounding skin protected by a cone of suitable size. Reaction occurs in about eight days, and the warts disappear in about three weeks. Those about the finger nails seem to be more resistant, and, if possible, the nailbed should be protected because reaction may cause deformity of the nail.

The treatment of deep plantar warts by irradiation is not so simple. The reaction to the infection is a growth of callus that may invade in a tack-like extension to considerable depth below the skin surface, even to the plantar fascia (fig. 6). This accounts for the severe and often disabling pain associated with them, especially when they are located over the heads of the metatarsals.

Superficial plantar warts can be treated successfully with contact x-ray therapy. If there is considerable callous formation over them this is shaved off with a scalpel, the lesions localized by metal cones, and one treatment of 2000 to 3000 r unfiltered radiation given. The reaction is a line of cleavage beneath the skin over the wart. The wart can be removed painlessly with a scalpel about three weeks after treatment.

In many cases plantar warts have penetrated so deeply, often to the plantar fascia, that they cannot be successfully treated by irradiation. Most of those which we have seen have been treated previously with topical application of caustic agents, roentgen therapy, and surgical operations. They are secondarily infected, consequently they do not respond to irradiation. The most successful treatment for deep plantar warts, developed by Dr. James A. Dickson of the Department of Orthopedics,[1] is removal of the toe and the metatarsal bone underlying the lesion. Although this seems to be a radical procedure it causes very little deformity of the foot, and results are most gratifying and are superior to any other therapeutic procedure.

FIG. 6. Photomicrograph of sagittal section of deep plantar wart extending tack-like to plantar fascia.

Local recurrences from carcinoma of the breast, if not too numerous or coalescent, yield satisfactorily to contact x-ray therapy. These lesions occur most frequently after operations on patients with involvement of the skin or muscles which cannot be, or have not been, removed. They may appear near the scar as small hard nodules a few weeks, months, or even years after operation, and the skin over them may be normal in color or red. They can be individualized and localized with suitable-sized cones for contact x-ray therapy and about 4000 r given with or without filtration, depending upon the size and depth of the nodules. Although the recurrences so treated will not recur, others or metastases usually develop later.

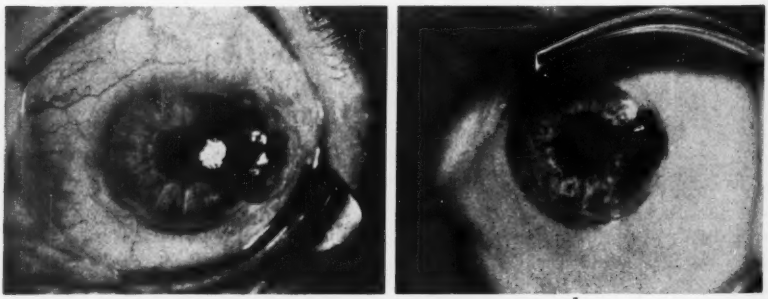
Superficial epitheliomas have been classified into three main types as basal cell, squamous cell, and mixed basal-squamous cell. There are variations of these according to clinical and histologic differences. It is often difficult,

a *b*

FIG. 7. (a) Epithelioma of skin of eyelid with involvement of lacrimal sac area. (b) Result after two years. No excessive lacrimation or recurrence.

if not impossible, to distinguish between different types of epitheliomas clinically.

Basal cell epitheliomas are the most common type. They usually occur in elderly people as single and occasionally multiple lesions on exposed skin of the face, ears, and hands, sometimes in relation to pre-existing keratoses. They start as painless, discrete, tiny, pearl-like papules which slowly enlarge and may ulcerate in the center. They are frequently thought to be "pimples." As the ulcer slowly enlarges the margins become elevated and rolled with pearly borders and covered by telangiectasia. Though they grow relatively slowly, if long standing or inadequately treated they will destroy underlying tissues, including cartilage and bone. Those that are extensive and ulcerative are called "rodent ulcers." They do not metastasize to adjacent lymph nodes.



a *b*

FIG. 8. (a) Squamous cell carcinoma of conjunctiva. (b) Result after two years. No recurrence or damage to eye. (Courtesy of DR. J. ROBERT ANDREWS.)

Squamous cell, or prickle-cell, epitheliomas also usually occur in elderly people on exposed surfaces and in relation to pre-existing keratoses. They are most common in people who are sensitive to actinic rays and who are constantly exposed to sunlight for many years, for example, farmers. Almost all epitheliomas occurring at mucocutaneous junctions about the mouth, anus, male urethra, and vulva are of the squamous cell type. The lesions may be papillary or sessile in growth characteristics and when sessile may simulate the basal cell type. The papillary type is less malignant than the sessile and does not tend to metastasize so early. These lesions begin as superficial ulcerations with crater formation, with or without a rolled pearly border, and considerably more induration is present than in basal cell epitheliomas. Some of the papillary type are cauliflower growths.

Small superficial basal and squamous cell epitheliomas without metastases can be easily and effectively treated with contact x-ray therapy. They are cancers, and therapy must be adequate. It is especially necessary to irradiate normal tissue well beyond the apparent borders of the lesions, because many have cutaneous or subcutaneous extension greater than can be detected clinically. The dose used is never less than 4000 r, and in many cases considerably more may be required, depending upon the depth of involvement. Filtration or increased distance and several fields may often be necessary.

The contact x-ray therapy is particularly useful for epitheliomas involving the eyelids (fig. 7), the conjunctiva (fig. 8), or lesions over bone or cartilage of the nose and ears because there is so little damage to underlying tissues. For deep, bulky, or extensive epitheliomas higher voltage x-ray therapy is preferable.

Reference

1. Dickson, J. A.: Surgical treatment of intractable plantar warts. Cleveland Clin. Quart. 13:92-95 (April) 1946.

HYPERVITAMINOSIS D

Report of 9 Cases

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HYPERVITAMINOSIS D may result from the prolonged use of vitamin D_2 and related sterols. The clinical manifestations of this condition include polydipsea, polyuria, muscular weakness, and headache, while less frequently drowsiness, nausea, vomiting, and diarrhea may appear. These symptoms are almost invariably accompanied by hypercalcemia and, at times, by widespread metastatic calcification in soft tissues. Since the kidney is particularly susceptible to metastatic calcification, serious impairment of renal function usually attends the intoxication and, if unrecognized, may prove fatal. It has been clearly demonstrated that all members of the vitamin D complex are capable of producing injurious effects.[1]

Case Reports

Case 1. A white man, aged 27, was first seen on October 29, 1946, because of severe rheumatoid arthritis of two years' duration. He had been taking vitamin D in capsules, but the exact form of drug, amount, and duration of treatment are not recorded. The patient had had an attack of "flu" five months previously, and since that time he had noted recurring headaches, muscle weakness, bouts of conjunctivitis, and increasing frequency and nocturia. Neither hematuria nor urethral discharge had ever been noticed.

On physical examination the weight was 145 pounds and the blood pressure 160 systolic, 90 diastolic. There was mild injection of the conjunctivae and a grade II constriction and sclerosis of the retinal vessels. No hemorrhages or exudate were noted. There was fusiform swelling of the first two fingers of the right hand, and the right knee was swollen. Anemia, proteinuria, azotemia, and impaired renal function were demonstrated. The blood urea measured 84 mg. per cent, and the urea clearance test gave values of 32 per cent and 36 per cent in the first and second hours, respectively. The urine had a specific gravity of 1.010 and grade II albumin. Blood studies revealed 3,900,000 red cells, hemoglobin 71 per cent, and 10,650 white cells. Blood calcium measured 14.5 mg. per cent, blood phosphorus 3.7 mg. per cent, and blood chloride 561 mg. per cent. Plasma proteins, using the Tiselius method, were normal. An intravenous urogram revealed poor renal excretion of diodrast. There was moderate calcification of the pelvic vessels (fig. 1), an interesting finding in a young person.

A diagnosis was made of rheumatoid arthritis with renal insufficiency due to vitamin D intoxication.

Six months following the withdrawal of vitamin D the patient had improved, and nocturia and polyuria had disappeared. An Addis test gave normal findings; blood urea was 45 mg. per cent, and urea clearance values were 62 per cent and 56 per cent in the first and second hours, respectively. There was no significant change in the calcification of the pelvic vessels.

Case 2. A white woman, aged 55, was admitted to the Cleveland Clinic Hospital on November 16, 1946, with an acute exacerbation of rheumatoid arthritis. She had had rheumatoid arthritis for ten years, and the shoulders, elbows, wrists, fingers, and knees were typically deformed. She had noted the onset of nocturia about one year prior to admission. This had progressed until she was urinating six or seven times each night. Fluids had been limited in an attempt to decrease this symptom. A long history of vitamin D intake was obtained. Six years previously she had taken 100 capsules (50,000 I.U. each) in divided doses, and three

FIG. 1. Case 1. Calcification of pelvic vessels in a 27-year-old man.

years later had resumed the drug, taking 300,000 units daily for two months. She was forced to discontinue the drug at that time because of nausea and vomiting. For the year and a half preceding admission to the hospital she had taken 150,000 units of vitamin D per day.

On examination the patient appeared chronically ill. The blood pressure was 120 systolic, 70 diastolic. There was grade II sclerosis of retinal arteries. A soft apical systolic murmur was present. The liver was palpable 3 fingers' breadth below the right costal margin, and the spleen was barely palpable. The joints in general were warm, and fusiform deformities were present. The proximal interphalangeal joints of the fingers were most involved.

Blood studies revealed 2,540,000 red cells, hemoglobin 7.7 Gm. (50 per cent), 9400 white cells, sedimentation rate 1.3 mm. per minute (normal up to 0.45 mm. per minute). The urine had a specific gravity of 1.011 and contained a trace of albumin. The Sulkowitch test* for urinary calcium was slightly increased. The blood urea measured 123 mg. per cent with urea clearance values of 11 per cent and 13 per cent in the first and second hours, respectively. Blood calcium levels were 10.7 mg. and 12.1 mg. per cent on two occasions, and blood phosphorus was 6.1 mg. per cent. Alkaline phosphatase was 3.7 Bodansky units. Values for total proteins were 7.5 Gm. per cent, and fractionation by the Tiselius electrophoretic method revealed a slight increase in the beta globulin fraction.

Roentgenologic studies revealed extensive calcification in the soft tissues about the shoulders (fig. 2) as well as in the aorta and the vessels of the thighs and pelvis. Calcification was present in the lower calyx of the left kidney. A large, sharply demarcated, calcific deposit was present just above the right greater trochanter (fig. 3). An intravenous urogram showed decreased diodrast clearance.

Subsequent studies of renal function following the withdrawal of vitamin D have not been possible.

**The Sulkowitch test is performed by the addition of an equal volume of reagent to urine. The reagent consists of:*

Oxalic acid	*2.5 Gm.*
Ammonium oxalate	*2.5 Gm.*
Glacial acetic acid	*5.0 Gm.*
Distilled water to make	*150.0 Gm.*

The degree of calciuria is estimated by the intensity and speed of formation of a fine white, flocculent precipitate.

FIG. 2. Case 2. Roentgenogram showing metastatic calcification in region of clavicles.

FIG. 3. Roentgenogram showing metastatic calcification in region of greater trochanter of femur.

Case 3. A white woman, aged 57, was first admitted October 25, 1946, complaining of nervousness and weakness of long duration. She had had unexplained stiffness and pain in her fingers and knees, for which Ertron, 200,000 to 300,000 units daily, had been prescribed. She had taken the drug intermittently for three years. In the two years preceding admission she had had recurring attacks of chills, fever, and dysuria. She had developed anemia in the previous six months, for which liver injections had been given. A hacking cough, a rather persistent conjunctivitis, muscular weakness, drowsiness, polyuria, and headache had appeared.

On examination the blood pressure was 150 systolic, 80 diastolic. The patient appeared chronically ill. A severe bilateral conjunctivitis was present. There was calcification of both tympanic membranes and hearing was poor. There was a grade II systolic murmur at the apex and diffuse tenderness in both costovertebral angles.

Laboratory studies disclosed moderate proteinuria, marked suppression of renal function, severe anemia, and hypercalcemia. Total blood proteins were 6.6 Gm. per cent, blood

calcium 14.0 mg. per cent, and phosphorus 4.0 mg. per cent. Hemoglobin measured 6 Gm. per cent (Haden-Hauser). Blood urea measured 84 mg. per cent, and urea clearance gave values of 13 per cent and 14 per cent in the first and second hours.

Vitamin D was discontinued and four weeks later urea measured 78 mg. per cent, and urea clearance test was 26 per cent and 30 per cent in the first and second hours. Blood calcium determinations were 13.5 mg., 13.8 mg., and 15.0 mg. per cent and blood phosphorus 4.4 mg., 5.2 mg., and 3.8 mg. per cent.

Roentgenologic studies disclosed areas of calcification in the costal cartilages and in the soft tissue overlying the greater trochanter of the left femur. Calcification was also present in the midline of the skull and was considered to be in the falx.

Six months later the patient was reported to be in good general health. Blood calcium and phosphorus levels were normal. Total blood proteins were 6.4 Gm. per cent, blood urea 23 mg. per cent, red blood count 2,700,000, and hemoglobin 58 per cent. Moderate proteinuria persisted. Roentgenologic studies showed calcification of the posterior tibial arteries and shadows suggesting early deposition of calcium in scattered areas.

Case 4. A woman, aged 54, was admitted in September, 1946, complaining of arthritis of the hands and feet of twenty years' duration. Headache, generalized muscular weakness, polydipsia, polyuria, and puffiness about the eyes had been noted, and an intravenous urogram, done elsewhere, had failed to demonstrate the kidneys. Hypertension and blurring of vision had been attributed to "kidney disease." She had taken vitamin D, 150,000 units daily, during June and July, 1946.

On examination the patient appeared chronically ill. Blood pressure was 160 systolic, 80 diastolic. Eye grounds showed grade II sclerosis of arteries, no hemorrhages or exudates. There was pain and tenderness in the knees and interphalangeal joints of the fingers. Heberden's nodes were present.

An Addis test revealed the urine to have a maximum specific gravity of 1.014; .08 Gm. of protein were excreted in twenty-four hours. Blood urea measured 45 mg. per cent, and urea clearance values were 25 per cent the first hour and 24 per cent the second hour. Red blood count showed 3,200,000 cells with 9 Gm. hemoglobin. Gastric analysis showed 41 per cent free acid. An intravenous urogram demonstrated poor renal function. Blood calcium and phosphorus levels obtained three months later gave values of 12.3 mg. and 3.0 mg. per cent, respectively. The blood urea at this time was 34 mg. per cent.

Case 5. A white woman, aged 52, was examined on May 13, 1947, because of rheumatoid arthritis of four and one-half years' duration. She had taken 4 capsules of Ertron daily from February to November, 1946, when she discontinued the drug because of nausea and vomiting. When these symptoms subsided she resumed the drug, taking 4 capsules daily, plus a weekly injection of Ertron for the next four months. She had noted generalized muscular weakness.

On physical examination the only positive finding was a grade III rheumatoid arthritis. Urinalysis disclosed a specific gravity of 1.008-10, and no sugar, albumin, or cells. Blood urea was 36 mg. per cent, and urea clearance values were 40 per cent the first hour and 42 per cent the second hour. Blood calcium was 11.5 mg. per cent, and phosphorus was 3.2 mg. per cent. The blood proteins were 7.6. The suppressed renal function and elevated blood calcium were attributed to vitamin D intoxication.

One month after withdrawal of the drug, the blood calcium was 10.5 mg. per cent, and phosphorus was 3.0 mg. per cent. Kidney function tests were not carried out, but there was no clinical evidence of renal failure, and the patient felt improved.

Case 6. A white woman, aged 34, was admitted on January 9, 1947, complaining of nausea and vomiting of all food, including gelatin and gruels. She had had a similar attack of nausea with vomiting one month before which lasted five days. For the previous one and one-half years she had had recurring bilateral frontal headaches. Polyuria, nocturia, muscle weakness, and drowsiness had appeared. There was no history of renal disease or infection; however, the patient had been taking daily doses of vitamin D for six weeks prior to admission to the hospital. Neither the exact amount nor the form of vitamin D taken was revealed.

Physical examination gave normal findings. Upon urinalysis, the Addis test demonstrated a specific gravity of 1.019 and normal amounts of casts and cells. Albumin was .288

Gm. per liter, sugar .219 Gm. per twenty-four hours. The Sulkowitch test showed increase in urine calcium. The white blood count was 6950, hemoglobin 9.5 Gm. (61 per cent), blood calcium 15.2 mg., phosphorus 2.4 mg., and urea 60 mg. Urea clearance was 30 per cent of normal. Wassermann and Kahn reactions were negative.

An intravenous urogram revealed poorly functioning kidneys, and a retrograde pyelogram gave normal findings. Cystoscopic examination was negative.

Vitamin D was discontinued, and there was a gradual return to almost normal kidney function eight months later. The only medication given was iron for the anemia. On January 30, 1947, the blood urea was 33 mg. per cent with urea clearance values of 47 per cent and 40 per cent in the first and second hours. Blood calcium was 10.5 mg. per cent, phosphorus 3.2 mg. per cent. On February 22, 1947, the blood urea was 24 mg. per cent with urea clearance values of 53 per cent and 58 per cent in the first and second hours. On August 9, 1947, blood urea measured 30 mg. per cent with urea clearance determinations of 82 per cent and 74 per cent in one and two hours, respectively.

Case 7. A white man, aged 60, was first examined on December 18, 1946, complaining of extreme thirst of five weeks' duration. He thought he had been drinking a gallon of water per day, and frequency in urination was present. Headache, nausea, vomiting, and blurring of vision had appeared. For the preceding ten days he had noted swelling of the legs, drowsiness, and generalized muscular weakness. Weight loss had been gradual but steady. He had been taking Ertron, 1 capsule three times daily, for the preceding ten months for a rather extensive hypertrophic arthritis.

On examination the blood pressure was 160 systolic, 72 diastolic. There was evidence of hypertrophic arthritis in the knees. There was grade I pitting edema over the sacrum and ankles. Peripheral arteries were hardened. Neurologic examination disclosed a slight nystagmus on lateral gaze, diminished vibratory sense in the lower part of his legs, and generalized motor weakness.

Laboratory studies revealed a blood calcium of 15.5 mg. per cent, and blood urea was 78 mg. per cent. Urinalysis was normal except for a specific gravity of 1010. Blood studies disclosed 4,400,000 red cells, hemoglobin 11.5 Gm. (74 per cent), and 9300 white cells. The basal metabolic rate was minus 13 per cent. Wassermann and Kahn reactions were negative. Spinal fluid gave normal findings.

Vitamin D therapy was discontinued and three weeks later the blood calcium was 12.0 mg. per cent, phosphorus 2.6 mg. per cent, and urea 45 mg. per cent. Ten months after his initial visit the patient felt completely well. Laboratory studies at this time revealed a blood urea of 30 mg. per cent with urea clearance values of 72 per cent in the first hour and 75 per cent in the second hour. Blood calcium and phosphorus levels were normal, being 10.8 mg. and 3.4 mg. per cent respectively.

Case 8. A white man, aged 53, was seen on March 31, 1947, complaining of low back pain of four months' duration. During this time he had been taking vitamin D, 350,000 to 500,000 units daily, until one week prior to admission. Two weeks before admission he had experienced a gastrointestinal upset, with nausea, vomiting, and constipation. Headache, polyuria, nocturia, muscular weakness, and nervousness had been constant.

Physical examination was negative except for poor posture and diffuse tenderness over the lumbar spine.

On laboratory examination the blood urea measured 54 mg. per cent, blood calcium 15.4 mg. per cent, phosphorus 3.5 mg. per cent, and urea clearance 26 per cent the first hour and 30 per cent the second hour. The urine at this time had a fixed specific gravity of 1.008. Roentgenologic studies revealed osteoarthritis of the lumbar spine.

One month after withdrawal of vitamin D, gastrointestinal symptoms disappeared. There was evidence of improving renal function, in that the blood urea was reduced to 39 mg. per cent, blood calcium was 11.0 mg. per cent, and phosphorus was 2.9 mg. per cent.

Three months later the patient was greatly improved and the nocturia had almost disappeared. Blood urea was 33 mg. per cent with clearance values of 112 per cent the first hour and 82 per cent the second hour. Blood calcium was 10.1 mg., phosphorus 2.9 mg.

Six months later an Addis count on the urine revealed a specific gravity of 1.022, protein 5.56 Gm. excreted in twenty-four hours, casts 200,000, red blood count 7,250,000, white

blood count 100,000. This was interpreted as evidence of inflammatory disease of the kidneys resulting from previous vitamin D intoxication.

Case 9. A white woman, aged 49, was admitted on October 14, 1944, because of nausea and vomiting of three weeks' duration. During this time she had suffered from recurrent headaches of excrutiating nature. She had also noted recent onset of nocturia, occurring twice nightly. She was unable to sit up in bed because of muscle weakness, and drowsiness was excessive. She had been taking 300,000 units of vitamin D daily for several months prior to admission.

On examination the blood pressure was 170 systolic, 110 diastolic. The eye grounds were normal. Heart and lungs were normal. There was no peripheral edema. The urine had a specific gravity ranging from 1.005 to 1.011, and there was a trace of protein in the urine.

Blood urea was 45 mg. per cent, and the urea clearance values were 36 per cent the first hour and 31 per cent the second hour. Plasma protein measured 5.4 Gm. per cent. Blood calcium was 11.9 mg. per cent and 11.3 mg. per cent, and the blood phosphorus was 2.8 mg. and 3.3 mg. per cent. Mild anemia was manifest, with hemoglobin of 68 per cent. Alkaline phosphatase measured 2.4 Bodansky units. An intravenous urogram showed poor clearance of diodrast. Roentgenologic examination disclosed calcification of the choroid plexus in the skull and generalized osteoporosis of the long bones.

A follow-up study after six months showed improvement in renal function, with a blood urea of 27 mg. per cent and a urea clearance of 56 per cent and 58 per cent in the first and second hours. The patient felt much better at this time.

Discussion

The calcium in the blood is contained entirely within the plasma. Quantitative determinations are best obtained from serum which normally contains from 9 to 11 mg. per 100 cc. This total serum calcium exists in two forms, an unbound, or ionizable fraction, and a protein-bound, or nonionizable fraction,

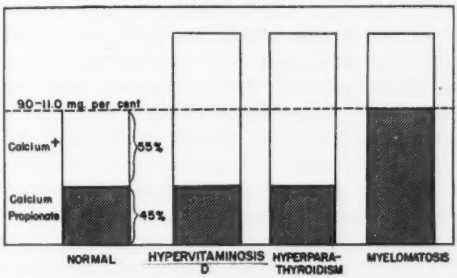

FIG. 4. Relation of calcium fractions in three diseases characterized by hypercalcemia.

attached principally to serum albumin. Under normal conditions these two forms are approximately equal in amount.

Abnormally high or low levels of serum calcium may result from an increase or decrease in either or both of these fractions. Although hypercalcemia is common in hyperparathyroidism, hypervitaminosis D, and myelomatosis, differences in the symptoms in these conditions may be partially explained in the alteration of serum calcium fractions (fig. 4).

The most prominent symptoms of hypervitaminosis D consist of polydipsia, polyuria, muscular weakness, and headache, and, less frequently, drowsiness, nausea, vomiting, and diarrhea. In hyperparathyroidism similar symptoms are

frequently manifest. In both of these conditions hypercalcemia is attributable to a rise in the ionizable calcium fraction, although the responsible mechanisms appear to be dissimilar. Total blood proteins are not increased in either. Furthermore, when hypercalcemia is corrected by either the withdrawal of the drug or the removal of a parathyroid adenoma, these symptoms disappear. Further, in myelomatosis, hypercalcemia, when present, is apparently due to an increase in protein-bound calcium and not to diffusable calcium. Polyuria, polydipsia, muscular weakness, and drowsiness are not outstanding symptoms in this condition. A relation between an increase in ionic calcium in the blood and common symptoms is strongly suggested.

However, toxic symptoms may appear at times in persons taking vitamin D in whom elevated blood calcium levels cannot be demonstrated.[2] It has been suggested, therefore, that vitamin D may be a primary irritant to tissue cells in some individuals and may be a factor more responsible for production of toxic manifestations than commonly considered.

The principal harm attending excessive administration of vitamin D is derived from metastatic calcification. If the drug is continued indefinitely irreversible damage to soft tissues, particularly the kidney, may ensue. Individual susceptibility to the drug is quite variable. Intoxication has been reported to result from as little as 1000 international units per kilogram per day.[3] On the other hand, it has been tolerated by others in doses up to 35,000 international units per kilogram per day.[4] In the patients studied by Reed *et al.*[3] symptoms of vitamin D toxicity occurred most frequently in those who also had gastrointestinal dysfunction such as diarrhea or constipation and, according to them, a number of factors influenced the toxicity of the vitamin. Included were the dosage per unit of body weight, the diet, purity of the vitamin, and the vehicle in which it is administered. The toxic property of the drug itself[5] depends in part upon the methods used to produce the drug. Frequent toxic effects which followed the use of ultraviolet-irradiated ergosterol were attributed to the large toxisterol content. The ergosterol which is activated by the electrical method of Whittier is considered to be somewhat less toxic. It would appear, however, that no form of vitamin D should be used indiscriminately.

The chief mode of action of vitamin D is to increase the absorption of calcium from the gastrointestinal tract. A consequent rise in diffusable calcium within the blood can thus be readily transferred to tissue cells. Widespread deposits of calcium presumably mobilized in this manner have been found in the various soft tissues. Experimental animals killed by sufficiently large doses of irradiated ergosterol repeatedly demonstrated diffuse metastatic calcification involving the arteriovascular system in the kidneys. Steck and his co-workers,[4] using dogs as experimental animals, fed them 20,000 to 1,000,000 international units per kilogram per day. Abnormally high levels of blood calcium appeared, and all died in coma when the drug was continued. Autopsy findings revealed the kidneys to be the most vulnerable organ. These workers hypothesized that the sequence of events included an initial injury to the tissue cells by the vitamin, followed by a deposition of calcium within the injured cells.

A case reported by Bauer and Freyberg[6] gives a striking example of metastatic calcification in the advanced stage of vitamin D intoxication. The arterio-

vascular system, the myocardium, lungs, and kidneys were sites of intense deposition of calcium salts. The kidneys were the most seriously involved, the renal arterioles being "primarily affected." The tubular and glomerular cells were less involved. The lumen of the tubules also contained calcium. Arterial calcification seemed to be limited to the media, the intima being spared in most instances.

Calcific deposition seems to be favored in acid-secreting cells with an alkaline reaction, such as in the kidneys, the lungs, and in the lining of the fundus of the stomach. Gough[6] and associates showed that the pH of excreted urine in some way altered the renal calcification of rats intoxicated with calciferol. Animals fed an acid ash diet developed different renal lesions than did those maintained on an alkaline ash diet.

Caution should be employed in the prolonged use of vitamin D in all persons because the individual susceptibility to the drug varies widely and because its optimum toxic effects may not be manifest for some months. Renal insufficiency should be regarded as a contraindication to the use of vitamin D. Blood calcium determinations should be made at repeated intervals on all patients taking vitamin D, since the cumulative action of the drug may not be detectable for many months. Only in this way will the early manifestations of hypervitaminosis D be recognized and the serious undesirable side-effects of metastatic calcification be prevented. Once induced, hypercalcemia, renal insufficiency, and metastatic calcification in other soft tissues may persist for many months after the drug is discontinued.

Summary

Roentgenologic evidence of metastatic calcification outside the kidneys was present in 2 of 9 cases of hypervitaminosis D. All 9 showed significant impairment of kidney function. Toxic symptoms included headache, nausea and vomiting, muscular weakness, drowsiness, polydipsia, and polyuria.

Discontinuance of vitamin D resulted in the disappearance of toxic symptoms in all cases. Kidney function improved significantly in the 7 cases in which follow-up studies were obtained.

In the 2 cases with metastatic calcification there was no evidence of roentgenologic improvement during the period of observation.

References

1. Freyberg, R. H.: Treatment of arthritis with vitamins and endocrine preparations; emphasis on their limited value. J.A.M.A. **119**:1165-1171 (Aug. 8) 1942.
2. Macrae, D. E.: Calciferol treatment of lupus vulgaris. Brit. J. Dermat. **59**:333-338 (Oct.) 1947.
3. Reed, C. I., Struck, H. C., and Steck, I. E.: Vitamin D: Chemistry, Physiology, Pharmacology, Pathology, Experimental and Clinical Investigations. (Chicago: University of Chicago Press, 1939).
4. Steck, I. E., Deutsch, H., Reed, C. I., and Struck, H. C.: Further studies on intoxication with vitamin D. Ann. Int. Med. **10**:951-964 (Jan.) 1937.
5. Bauer, J. M., and Freyberg, R. H.: Vitamin D intoxication with metastatic calcification. J.A.M.A. **130**:1208-1215 (April 27) 1946.
6. Gough, J., Duguid, J. B., and Davis, D. R.: Renal lesions in hypervitaminosis D.: observations on urinary calcium and phosphorus excretion. Brit. J. Exper. Path. **14**:137-145 (June) 1933.

TETRAETHYLAMMONIUM CHLORIDE IN MULTIPLE SCLEROSIS

A Preliminary Report

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DIRECT observation of the blood vessels in the central nervous system during sympathetic stimulation or after the injection of various drugs is the subject of a number of published reports. Most convincing are the observations made by Franklin and Brickner,[1] who have relieved retinal vasospasm and scotomas simultaneously by the use of amyl nitrite or intravenous papaverine. They postulate that lesions of multiple sclerosis result from, or are associated with, vasospasm, that scotomas in patients with multiple sclerosis are the result of vasospastic lesions in the retina, and that such disturbances apply with equal validity to any portions of the central nervous system.

Lyons *et al.*[2] have demonstrated that tetraethylammonium chloride is capable of relieving vasospasm in man by blocking the autonomic ganglia. If there is some truth to the assumption that the acute or the exacerbative symptoms of multiple sclerosis contain the element of vasospasm, tetraethylammonium chloride may produce a modifying influence upon these acute symptoms in perhaps the same fashion as do the injections of histamine by Horton, Wagener, Aita, and Woltman.[3]

Several recent articles on the treatment of multiple sclerosis have suggested that, irrespective of the underlying cause, one factor in the disease is some vascular disorder such as a venous stasis or change in vasomotor tone. Such hypotheses form the basis for the use of histamine and dicumarol.

In pursuance of this hypothesis tetraethylammonium chloride has been administered to a number of patients manifesting the acute and chronic symptoms of multiple sclerosis. All of the patients have a history of exacerbations and remissions of the disease.

The technic of administration consists of a deep intramuscular injection of tetraethylammonium chloride, 500-1200 mg. (Etamon*), three to six times per week. The immediate outstanding effects of the drug are an orthostatic hypotension and a loss of visual accommodation. The patient should remain in a supine position for one hour after treatment to avoid syncope and dizziness. Blood pressure readings are taken at five-minute intervals for one-half hour.

Fourteen patients who displayed the familiar acute manifestations of multiple sclerosis, such as transient scotomas, diplopia, numbness, paresthesias,

* *We wish to acknowledge the donation of the drug used in part of this study by Dr. E. C. Vonder Heide, Parke, Davis and Company.*

weakness of the extremities, urinary incontinence, dysarthria, astereognosis, and ataxia, were treated. Continued treatment with tetraethylammonium chloride in all instances appears to have protected our patients so far from either relapses or further progression of symptoms. Intermittent scotomas were promptly relieved in 1 patient after injection of the drug. In this series the longest period of freedom from acute symptoms has been five months. In 1 patient who refused prolonged treatment there has been no evidence of relapse over a period of six weeks.

The pharmacologic action of tetraethylammonium chloride does not indicate that this drug would be of any benefit in preventing further relapses once medication has been discontinued. The small number of patients and brief period of observation does not offer convincing proof that the drug entirely controls the transitory symptoms of multiple sclerosis. Nevertheless, the fact that all 14 patients with acute symptoms began to show definite improvement of the most recently acquired manifestations within four days after onset of treatment seems significant. Furthermore, none of the members of this group became subjectively or objectively worse after therapeutic doses of tetraethylammonium chloride had been initiated.

The spontaneous and unpredictable remissive factor in multiple sclerosis is well known. Claim as to the value of the treatment, therefore, lies in the improbability that fourteen spontaneous remissions would have occurred within four days after onset of therapy.

The acute symptoms of multiple sclerosis responded to this therapy. Eight patients, whose chronic manifestations had been unvarying for six months or more prior to treatment, were not benefited. These studies indicate that the features of multiple sclerosis which have endured longer than two or three months are not relieved by injections of tetraethylammonium chloride. Therefore, early diagnosis appears to be of great importance if this type of therapy is to be of value.

The small series of patients and the brief time factor involved necessitate a cautious interpretation of the results. The experiences recorded, however, do suggest that the acute and newly-superimposed symptoms of multiple sclerosis may be subjectively and objectively modified by tetraethylammonium chloride. Therefore, it can be argued that the therapeutic value of this drug, like that of histamine and of dicumarol, is based on its ability to interfere with one of the pathologic features of multiple sclerosis.

References

1. Franklin, C. R., and Brickner, R. M.: Vasospasm associated with multiple sclerosis. Arch. Neurol. & Psychiat. **58**:125-162 (Aug.) 1947.
2. Lyons, R. H., *et al.*: Effects of blockade of autonomic ganglia in man with tetraethylammonium; preliminary observations on its clinical application. Am. J. M. Sc. **212**:315-323 (March) 1947.
3. Horton, B. T., Wagener, H. P., Aita, J. A., and Woltman, H. W.: Observations on treatment of multiple sclerosis by intravenous administration of histamine. Proc. Central Soc. Clin. Research **16**:23-24, 1943.

ECHINOCOCCUS CYST OF THE LIVER

Report of 4 Cases

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ECHINOCOCCUS disease is a parasitic disorder seldom encountered in the United States. The condition is also known as echinococcus cyst, hydatid cyst, echinococcosis, and hydatidosis. It is characterized by cystic lesions in the liver and lungs resulting from the infestation of Taenia echinococcus, and by lesions which are not truly cystic in some other organs, such as the bone and the brain. For this reason, many writers prefer the name echinococcosis or hydatidosis.

The etiologic agent is Taenia echinococcus, or the dog tapeworm.[1] It is a cestode morphologically similar to other tapeworms, having a head with suckers and hooklets and segments of its body called proglottids (usually three, sometimes four or five). The terminal proglottid contains the ova. The eggs, which resemble those of T. saginata, the beef tapeworm, are emptied into the bowel lumen of the definitive host by the adult taenia which is present in the small bowel. The definitive host for this parasite is usually a dog but may be a wolf, cat, or some other carnivorous animal. The ova are deposited with the feces of the host. The fecal material containing the ova contaminates grass, vegetables, or water, and by ingesting such substances, the intermediate host is infested. The intermediate host is usually a sheep or other mammal, such as man. Human beings are believed to become infested principally by contact with dogs.

Upon ingestion the parasite ovum proceeds down the digestive tract of the intermediate host and loses its membrane in the alkaline medium of the small bowel. The hexacanth embryo thereby liberated then attaches to the villi of the small bowel, penetrating the wall and entering a capillary vessel. The embryo is then carried to the liver directly by the blood stream, where it is filtered out by a hepatic lobule, setting up a focus in the liver. However, the embryo may pass through the liver and lodge in a capillary bed elsewhere, such as in the lungs, spleen, kidneys, bone, or brain. A second route of transmission to the lungs is by direct boring through the tissues, which would account for the high percentage of involvement in the right lower lobe of the lung.[2]

Involvement of various parts of the body by T. echinococcus is roughly as follows (Arce):[3]

Liver	70%	Kidneys	2%
Lungs	15%	Brain	2%
Muscles	4%	Connective Tissue	2%
Spleen	3%	Bone	2%

The embryo grows into a larva by a process of vacuolation, forming a vesicle full of fluid with a surrounding germinal epithelium and outer cuticular membrane. By a process of invagination and sometimes evagination from the germinal epithelium of the mother cyst, daughter cysts and eventually granddaughter cysts are formed, having characteristic scolices with a double row of hooklets. As these scolices grow they detatch themselves from the vesicle and drop free into the sac of the mother cyst. These larvae are commonly known as "hydatid sand."

The cysts in the liver are usually single and unilocular, but in some instances may become multilocular due to evagination of the germinal epithelium and development of daughter cysts. These may pinch off and become separated. When cysts do not separate completely from the growth the vesicles frequently look like a bunch of grapes projecting from the main mass (fig. 2a).

With increasing age and growth of the cyst (which is generally slow), there is degeneration of the parasite, rendering it more susceptible to infection. The infection may be either blood-borne or derived from a bile passage into which the cyst may have eroded. These conditions are uncommon. There may be deposition of calcium in the parasite also, but this is usually minimal and not enough for demonstration by roentgenologic examination, at least until late in the process.[4,5]

The mother cyst or sac has two layers, an inner germinal layer and an outer chitinous or cuticular membrane. The outer membrane has a characteristic laminated structure. The cyst causes a foreign body reaction in the organ (especially true in the liver) and thereby causes the production of a connective tissue layer (or adventitia) around the sac. With the growth of the cyst there is atrophy of the surrounding organ, aiding in the production of the connective tissue capsule. Obliteration of the small vessels by this increase in size leads to endarteritis and diminished blood supply to the capsule.

This relatively avascular fibrous capsule may become necrotic in areas and frequently shows hyaline degeneration. As in degenerated tissue anywhere in the body there may be a deposition of calcium in it. This deposition of calcium in the fibrous capsule is a late manifestation and is indicative of senility of the cyst.[4]

Complications which occur with this disease are trauma and infection.[4,6] If the cyst wall is broken the larvae may be released into the peritoneal cavity and encyst on the omentum, peritoneum, pelvis, or elsewhere. There may be extension in such a manner through the diaphragm into the lung.[3] Infection usually causes death of the cyst, and the resulting symptoms are similar to other infections of the liver.

Location of cysts in the liver are, according to Arce,[6] 85 per cent in the right lobe and 15 per cent in the left lobe. Central or peripheral location within a lobe is of great importance in both diagnosis and treatment. Those which are immediately subphrenic often give rise to few or no signs readily accessible on physical examination. They may, however, cause elevation and diminished excursion of the right leaf of the diaphragm and even diminished aeration of the right base of the lung.

Classical areas in which echinococcosis is to be found are Iceland, Australia, New Zealand, Argentina, and Uruguay.[4,7] In Iceland 50 cases were reported in 1925; in Argentina one man reported 128 cases from his clinic in three years; in Uruguay incidence is reported as 1 case in every 187 persons. Other endemic areas are Southern Germany, Russia, the Balkan states, and Mediterranean countries, such as Spain and parts of Italy, Greece, Syria, and North Africa. India is an endemic area, and some cases have been reported from Japan. Until recently North America was considered the site of echinococcosis only by virtue of immigration from endemic areas.[8,9] Magath[7] reported that 482 cases were recorded in the North American literature from 1880 to 1936 and of these only 22 were natives of the United States or Canada. Hudson[10] reports a cyst in a 67-year-old woman who had been born in Atlanta, Ga., and lived in that city all of her life. She supposedly had not had contact with farm animals but had intermittently kept pet dogs and cats in her home. Hudson found a high incidence of infected livers among the animals at a local slaughter house.

Diagnosis

Diagnosis is based on clinical, roentgenologic, serologic, and blood findings.

The most common symptom is pain. There may be only a feeling of discomfort, or the pain may be sharp and similar to that of gallbladder colic. Radiation of the pain to the back or to the right shoulder occurs frequently and was observed in 2 of our cases. All of the patients reported in this paper had pain as a major symptom. Jaundice occurs frequently (seen in 3 of these 4 cases) and is similar to that produced by a stone in the common duct. The stools may become light-colored and the urine dark. Evidence of a mass in the upper abdomen may be present. Diminished aeration of the right lung is noted in some cases when the cyst is located near the diaphragm or when the liver-cyst mass is quite large. Intolerance to fatty foods and belching are frequent symptoms. When there is rupture through the diaphragm, evidence of pleuritis, coughing, hemoptysis, and expectoration may be present. Scolices may be expectorated and in such cases a definite diagnosis may be established by sputum examination.

Blood and serologic findings include eosinophilia, positive complement fixation test, and positive skin test. Eosinophilia is least constant (about 25 per cent of cases), is present in the early stages, and diminishes or disappears when the cyst becomes senile. Complement fixation test (Imaz-Lorentz) is similar in type to the Kolmer-Wassermann test and is generally positive in about 60 per cent of cases, according to Arce.[6] The cutaneous reaction test of Casoni is considered most reliable and is positive in about 90 per cent of the cases.[6,11]

Roentgenologic evidence of hydatid or echinococcus disease of the liver is based on the demonstration of abnormal changes in the right upper abdomen. Direct roentgenologic evidence is present when calcification within the liver shadow or a soft tissue mass attached to the liver can be observed.[8,12] Calcification of the capsule is usually not homogeneous or symmetrical, and the mass may appear quite irregular. The calcification may be a massive solid-appearing

concrement, as reported in one of the cases of G. Claessen[4] from Iceland. Because of this variation early diagnosis based on calcification of the fibrous capsule is not easy. The calcific shadow may extend beyond the liver shadow, or a soft tissue shadow produced by a cyst may extend beyond the liver border.

Indirect roentgenologic evidences of an echinococcus cyst of the liver are hepatomegaly, elevation of the right leaf of the diaphragm, and calcification of a cyst in the abdomen extrinsic to the liver. Though a cyst in the liver may be quite small, there may be an associated hepatomegaly. Some believe that liver enlargement is a compensatory phenomenon. One patient in our group had an enormously enlarged liver with a fairly large cyst in the left lobe and some small cysts in the right lobe.

When the cyst is subphrenic the diaphragm is frequently elevated, and there may be suggestive evidence of some atelectasis at the right base. If the cyst has ruptured through the diaphragm, pleural change, evidence of fistulous tracts, and later calcific infiltration in the thorax may occur.

Calcification of a cyst elsewhere in the abdomen or evidence of an echinococcus cyst in other organs of the body suggests the possibility of the same disease in the liver.[13,14] G. Claessen[4] reports a case in which there was a large cyst in the pelvis with infestation also present in the liver.

Four cases of echinococcus disease of the liver have been seen at the Cleveland Clinic. The important diagnostic features of these will be briefly summarized.

Case Reports

Case 1. A woman, aged 42, had had pain in the right shoulder for six weeks. This pain radiated into the neck and was aggravated by deep breathing, coughing, and by torsion of the trunk. Slight nausea and some vomiting had been present. There was no history of jaundice or of intolerance to fatty foods. The patient had been born in Italy and resided there for thirty-nine years before coming to the United States.

On examination the liver was palpable 3 fingers' breadth below the right costal margin. It was rounded, somewhat nodular, and interpreted as an enlarged gallbladder with a Riedel's lobe. Pressure over the mass produced typical pain in the shoulder. Diminished breath sounds and dullness on percussion were noted in the right lower thorax. Routine blood studies were normal; eosinophil count was 4 per cent. Urine studies were normal. Complement fixation and skin tests for echinococcosis were not done. Roentgenologic examination demonstrated elevation of the right diaphragm, nonvisualization of the gallbladder, and normal gastrointestinal tract. The patient was placed on a course of anti-amebic therapy without relief. At operation a large cyst in the posterior portion of the right lower lobe of the liver was evacuated. Typical echinococcus larvae with scolices and double rows of hooklets were found, and the characteristic cyst wall was demonstrated on pathologic examination. The cyst cavity was packed. Symptoms diminished but did not disappear completely.

Case 2. A woman, aged 41, whose birthplace and residence prior to entering the United States are not known, had complained of a "sour stomach" and nonradiating pain in the right upper abdomen for many years. These attacks of pain were associated with a sense of fullness in the epigastrium and were aggravated or initiated by eating fatty foods. On occasions jaundice was present.

The liver was palpable 3 fingers' breadth below the costal margin. Blood studies were normal, with eosinophil counts of 1 and 3 per cent. Routine urine studies were normal. Liver function test showed no evidence of dysfunction. Complement fixation test was not done, but the skin test was positive at five and thirty minutes. Roentgenologic examination demonstrated a large mass containing calcium in the right upper quadrant. The mass was

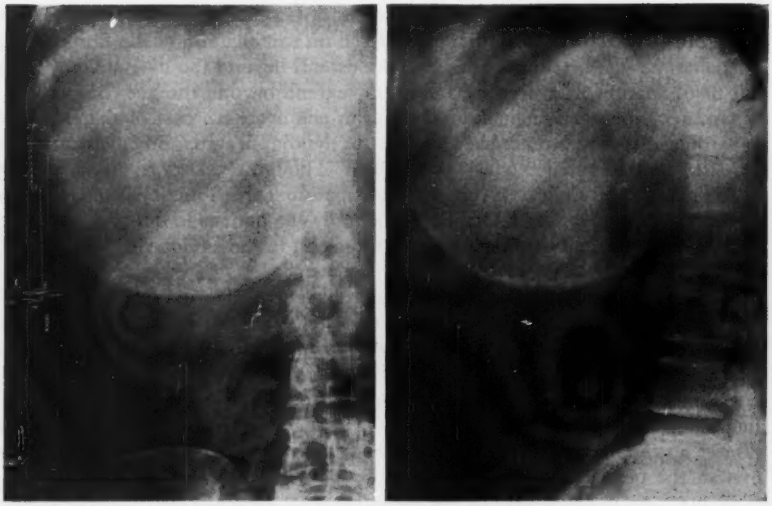


FIG. 1. Postero-anterior and lateral roentgenograms demonstrating irregularly calcified mass in liver. Mass measured approximately 19 cm. in diameter on film.

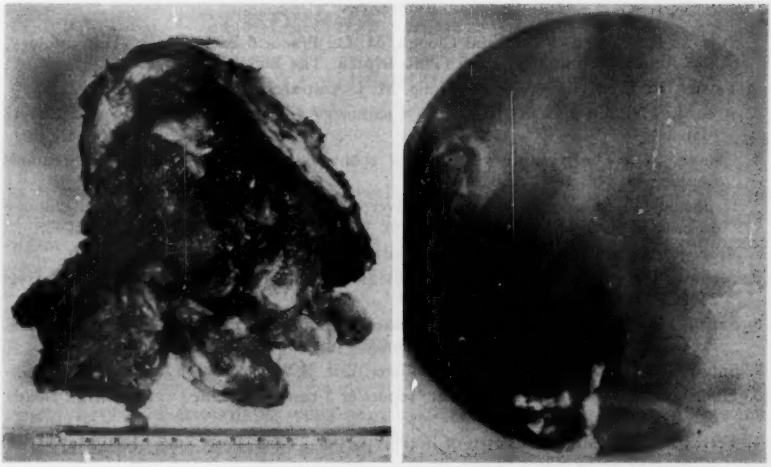
round, and its diameter measured approximately 19 cm. (fig. 1). The gallbladder was visualized on cholecystographic examination. At operation a large cyst in the inferior portion of the right lobe was evacuated and packed with formalin gauze. Diagnosis of echinococcus cyst was confirmed by pathologic examination. Follow-up showed that the patient had diminished pain and had had no recurrence of jaundice.

Case 3. A boy, aged 16, had had attacks of epigastric pain with occasional vomiting and occasional pain in the right shoulder for two years. On at least two occasions he was jaundiced and noted light-colored stools and dark urine at the time of the attacks. Intolerance to fatty foods was present. He had had no chills or fever. The patient had been born in Italy and had lived there for three and one-half years before coming to the United States.

The liver edge was palpable, and fullness in the epigastrium was noted on examination. Blood studies showed a white blood count of 7250 with 19 per cent eosinophils. Liver function tests were not done. Routine urine studies were normal. Complement fixation tests and skin tests were not made. Roentgenologic examination showed no calcification in the right upper quadrant. On gastrointestinal study there was displacement of the barium-filled first and second portions of the duodenum to the left by the enlarged liver. The gallbladder was not visualized on cholecystographic examination. At operation the right lobe of the liver was found to be tremendously enlarged, and the left lobe was slightly enlarged. Small cysts were present in the right lobe, and a large cyst was present in the central portion of the left lobe. Diagnosis of echinococcus cyst was confirmed by pathologic examination. The cyst was marsupialized and the cavity filled with formalin packs. Since the cyst has filled in there has been no recurrence of symptoms.

Case 4. A man, aged 56, complained of "gallbladder trouble," having had attacks of severe nonradiating epigastric pain for several years. Jaundice was associated with these attacks, but no nausea or vomiting had been noted. There was no intolerance to fatty foods. The patient had been born in Italy and came to this country at the age of 5 or 6.

The patient had had an operation, evidently a cholecystostomy, four years previously, at which time some stones were said to have been removed. Relief of symptoms followed for



a *b*

FIG. 2. (a) Surgical specimen, demonstrating thickened adventitia and grape-like vesicles. (b) Roentgenogram showing partially calcified mass extending beyond liver shadow.

about two years, after which they recurred. One year before his visit to the Clinic he was told that x-ray examination showed some "crystals in the liver." On examination the liver was barely palpable. Blood studies were within normal limits except for an eosinophil count of 6 per cent. Routine urine studies were normal. Complement fixation and skin tests were not made. Roentgenologic examination demonstrated a large soft tissue mass in the right lobe of the liver which extended beyond the liver border (fig. 2). Most of the mass was outlined by flecks of calcium around its periphery. The gallbladder was not visualized on cholecystographic study. At operation a large cyst encountered in the right lobe of the liver was evacuated and its wall cauterized. Pathologic studies confirmed the diagnosis of echinococcus cyst. The postoperative period has been too brief for follow-up.

Summary

Four cases of echinococcus cyst of the liver seen at the Cleveland Clinic are reported. All of these patients had pain referable to the right upper quadrant and other symptoms similar to those of gallbladder disease. Three had been jaundiced, and 2 of these were intolerant to fatty foods. All of these patients had hepatomegaly but no evidence of liver damage. Only 1 had significant eosinophilia. Eosinophilia would not be expected in the other cases since the infestation was most likely of quite long standing. Two of the cases showed calcification of the adventitia indicative of an old infestation. The skin test is the most accurate diagnostic test available but was performed in only 1 of the 4 cases reported.

Surgical evacuation at least partially relieved the symptoms in the patients we have been able to follow.

References

1. Stitt, E. R., Clough, P. W., and Clough, M. C.: Practical Bacteriology, Haematology, and Animal Perisitology, ed. 9 (Philadelphia: The Blakiston Co., 1943).
2. Fairley, K. D.: Hydatid disease of lung. M. J. Australia **1**:346-355 (April 1) 1922.
3. Arce, J.: Hydatid disease (hydatidosis): pathology and treatment. Arch. Surg. **42**:1-17 (Jan.) 1941.
4. Claessen, G.: The roentgen diagnosis of echinococcus tumors; a study. Acta radiol. Supplement No. 6, 1928.
5. Heilbrun, N.: Massive calcification of liver; case report with discussion of its etiology on basis of alveolar hydatid disease. Am. J. Roentgenol. **55**:189-192 (Feb.) 1946.
6. Arce, J.: Hydatid cyst of liver. Arch. Surg. **42**:973-987 (June) 1941.
7. Magath, T. B.: Hydatid (Echinococcus) disease in Canada and United States. Am. J. Hyg. **25**:107-134 (Jan.) 1937.
8. Smith, H. L., and Magath, T. B.: Calcified echinococcus cysts in liver; report of case. Proc. Staff Meet. Mayo Clin. **12**:405-408 (June 30) 1936.
9. Smyth, M. J.: Calcified hydatid cyst of liver. Brit. J. Surg. **27**:604 (Jan.) 1940.
10. Hudson, P. L.: Echinococcus disease; report of 3 cases of calcified cysts of liver. South. M. J. **38**:584-589 (Sept.) 1945.
11. Ferris, D. O.: Echinococcus cysts of liver; report of 2 cases. Proc. Staff Meet. Mayo Clin. **15**:345-349 (May 29) 1940.
12. Leader, L. O., and Goldberg, G.: Echinococcus cyst of left lobe of liver; report of case. Am. J. Roentgenol. **44**:207-208 (Aug.) 1940.
13. Cunniffe, E. R.: Double echinococcus cyst of liver treated by marsupialization. Ann. Surg. **101**:1442-1447 (June) 1935.
14. Steinke, C. R.: Echinococcal cyst (hydatid) of spleen and liver; report of 2 cases. Am. J. Surg. **57**:544-547 (Sept.) 1942.

TUMORS OF THE ORBIT

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TUMORS of the orbit are not uncommon and must be suspected in every patient with exophthalmos, especially if the condition is unilateral. Benign tumors are the most frequent and include hemangioma, pseudotumor, meningioma, dermoid cyst, osteoma, neuroma, and lipoma. The malignant growths are sarcoma, carcinoma (frequently of the lacrimal gland), lymphoma, leukemic infiltrations, and tumors of the optic nerve.

Clinical Manifestations

The most consistent finding in patients with orbital tumors is exophthalmos, which may be a straight forward protrusion if the growth arises within the muscle cone of the eye or a lateral or vertical displacement if the tumor arises from outside this area. Tumors arising in the anterior half of the orbit usually displace the globe to the opposite side and may produce little or no real exophthalmos. The amount of forward displacement of the eyeball can readily be measured with a Hertel's exophthalmometer; 15 - 20 mm. is usually considered normal. Pain is not a common symptom, and congestion of the conjunctiva occurs but rarely, although it may be present in vascular tumors.

Diplopia resulting from proptosis and the resulting immobilization of the eye may not be apparent to the patient because of visual impairment of the affected eye. Visual field defects and loss of visual acuity occur early in tumors invading the optic nerve or optic canal and may occur later in tumors of other parts of the orbit that produce pressure on the optic nerve or globe due to their increased size.

Incidence

The most common orbital tumor is the hemangioma, which is a benign type of growth, is usually well encapsulated, and, though it produces exophthalmos, has little effect on ocular motility. Reese[1] reports 25 in a series of 174 cases of tumor of the orbit. Meningioma and pseudotumor occur next in frequency. The pseudotumor is a little-known tumor and is usually thought to consist of chronic inflammatory tissue. Most of these tumors progress in size to produce exophthalmos and diplopia.

Other tumors occurring frequently are the dermoid cyst, neurofibroma, sarcoma and glioma, and mixed tumors of the lacrimal gland. Of the latter Reese[1] found 9 in his series of 174 cases.

Orbital tumors seldom occur bilaterally, but when they do they are usually of the leukemic infiltration type.

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Diagnosis

As an aid to diagnosis the following procedure is usually employed: the visual acuity, visual fields, fundus examination, refraction, and muscle balance are first evaluated. By palpation and use of the stethoscope, the tumor is then localized, its consistency is determined, if possible, and bruit and pulsations are ruled out. If a systemic disease is suspected as the underlying cause, a general examination together with complete blood study and basal metabolism test is carried out. A most valuable adjunct to diagnosis is a roentgenogram of the orbit and its surrounding structures. A biopsy, either by aspiration or by operation, may be performed, although this procedure is not often done.

Differential Diagnosis

There are numerous diseases that produce exophthalmos and otherwise simulate orbital tumors.

Exophthalmos caused by high myopia, 25 or more diopters, must be excluded. This condition may be unilateral or bilateral. Early hyperthyroidism with exophthalmos sometimes affects one eye earlier than the other. The method of determining these entities is self evident. Diseases of the accessory sinuses, such as pyocele, mucocele, and hyperostosis of the orbital walls, frequently result in exophthalmos; these may be ruled out by roentgenologic examination. Diseases such as Mikulicz's disease, Hodgkin's disease, xanthomatosis, and syphilis sometimes are confusing and require complete medical evaluation. Pseudotumor, thrombosis of cavernous sinus, and orbital cellulitis cause exophthalmos and usually pain and fever and can be suspected because of the associated symptoms. An aneurysm, either traumatic or due to vascular anomaly, is manifested by a pulsation and bruit over the involved eye.

Treatment

Therapy depends upon the final diagnosis, although treatment is primarily surgical. If all medical causes have been ruled out and differential diagnosis cannot be made, and there is danger to visual acuity, surgical exploration should be done.

The Kronlein[2] operation has been recommended as the best means of exposing a tumor in the orbit, although this procedure is usually unnecessary; a transconjunctival incision either at the external canthus (with an external canthotomy and resection of the external rectus muscle, if necessary) or an incision in the superior or inferior cul-de-sac is frequently adequate to expose and remove the growth. If the growth appears malignant a specimen of tissue can be removed for microscopic examination. Excision of the growth, enucleation of the eye and the growth, or exenteration can then be done.

Certain tumors, such as the leukemic infiltrations, the xanthomatoses, and pseudotumors, are amenable to x-ray therapy. These are not always diagnosed prior to microscopic examination.

Case Reports

The following 3 cases of rare tumors, a nerve sheath tumor, an adenocarcinoma of the lacrimal gland, and a lymphosarcoma, have been treated in the Department of Ophthalmology during the past year.

The nerve sheath tumor (neurilemmoma) occurs rather infrequently. Reese[1] mentions one in his series of cases, and Rottino and Kelley[3] in 1941 reviewed the literature and found but 11 cases reported. They occur at almost any age between 2 and 70 years. Growth is usually progressive.

Case 1. Neurilemmoma. A white woman, aged 50, was admitted to the Department of Ophthalmology on February 11, 1947, complaining of the recent onset of sharp pain in the left side of the face and prominence of the left eye of five years' duration. There was no visual impairment or diplopia. (Figure)

External examination revealed pressure which was forcing the left eye superiorly and temporally and a moderately firm mass just below the eyeball. The anterior-posterior measurement was O.D. 17 mm., O.S. 22 mm.

FIGURE. Case 1. Patient with neurilemmoma of left orbit.

On ophthalmologic examination the visual acuity was O.D. 6/9-2, O.S. 6/12-1, the fundi were normal, and the muscle balance test revealed exophoria of 16 diopters and left hyperphoria of 1 diopter.

Roentgenologic examination revealed some increased density of the left maxillary sinus. Roentgenograms of the teeth gave normal findings. Except for the findings in the left antrum, the ear, nose, and throat examination was negative. Blood and urine were normal. A preoperative diagnosis of tumor of the left orbit was made. On April 7, 1947, a transconjunctival incision at the external aspect of the left eye with an external canthotomy was made, and a small, well-encapsulated tumor was removed *in toto*.

The gross specimen was an ovoid mass measuring 25 by 15 by 10 mm., encapsulated, and of soft consistency. Tags of fibrous tissue were present on the surface. On section there was a cystic structure 9 mm. in diameter. The tissue was semitranslucent, grayish-yellow to pink in color, and soft and friable in consistency.

On microscopic examination the mass was rather cellular, but there were patches of loose arrangement and slight cellularity. Cells were small, of spindle shape, and arranged in sharply interlacing bundles, and there were frequent areas of nuclear palisading. The tissue bordering the cystic structure was of loose arrangement, and the vessels were moderately numerous, showing thick hyaline walls. There were occasional mitoses. A thin but well defined fibrous capsule was present. A diagnosis of neurilemmoma was made.

The postoperative course was uneventful. When last seen at the Clinic the patient complained of diplopia, and muscle measurement still showed a pronounced error. There was no evidence of recurrence of the tumor.

Lymphosarcoma is also a rare tumor. In Reese's[1] series it occurred in 5 cases, and Dandy[4] in his monograph on 31 cases of orbital tumors mentions but 1 case (round cell sarcoma), Iles and Short[5] had no incidence of lymphosarcoma in their series of 14 cases, 3 of which were malignant. This type of tumor usually occurs in later life, the average age being 55 years. It is highly malignant and radiosensitive but unfortunately is only one manifestation of a fatal systemic disease.

Case 2. Lymphosarcoma. A white man, aged 66, was first seen on June 2, 1947, complaining of a growth which had been present on the lateral aspect of the left eyeball for the past five weeks. It caused him to see double on reading or looking to the left. The patient had no pain and did not think his vision was affected. He believed that the growth had increased rapidly in size since he had first noticed it.

External examination revealed a rather firm subconjunctival mass on the temporal side of the left eyeball which seemed to arise inferiorly. No exophthalmos was observed.

On ophthalmologic examination the visual acuity was O.D. 6/6-4, O.S. 6/6-4, and the fundi were normal.

The blood counts were essentially negative except for a slight poikilocytosis; the leukocyte count was 9600. Roentgenologic examination of the chest revealed bilateral infiltration which was thought to be consistent with an old acid-fast lesion.

A preoperative diagnosis of subconjunctival tumor was made, and on June 7, 1947, a friable tumor mass was removed with some difficulty from the inferior temporal aspect of the left eyeball. The tumor tissue appeared to be infiltrating the globe.

The gross specimen consisted of many small portions of tissue, the largest measuring 9 mm. in diameter. Fragments varied from fairly firm to soft texture and were of yellowish-pink color. Several smaller portions were composed of fat and fibrous tissue.

On microscopic examination the fragments were formed principally of striated muscle and there were areas of dense infiltration by small round cells with round nuclei. A moderate number of mitoses were present, and a few eosinophils were found.

A diagnosis of lymphosarcoma was made.

The immediate postoperative course was uneventful, and 250 r was given on each of the ten successive days. Examination for lymphadenopathy elsewhere in the body revealed only two small affected glands in the right groin. A guarded prognosis was given; however, a communication from the patient six months later stated that he was feeling well.

Mixed tumors of the lacrimal gland may occur as adenocarcinoma, and when the epithelial element predominates these are sometimes known as cylindromas. Although this is a carcinomatous tumor it is usually well encapsulated. It usually occurs in persons of middle age or older.

Case 3. Adenocarcinoma of lacrimal gland. A white woman, aged 43, reported to the Department of Ophthalmology on February 24, 1947, giving a history of prominence of the left eye of eight months' duration. No visual impairment or diplopia had been observed. Four months previously she had noticed sharp pains around the left side of the forehead and the left eye.

External examination revealed exophthalmos of the left eye, and a small mass could be palpated under the upper lid. Anterior-posterior measurements were O.D. 19, O.S. 21.

On ophthalmologic examination the visual acuity was O.D. 6/6-3, O.S. 6/6-3. The fundi were essentially normal, and the muscle balance test showed exophoria of 6 diopters for near and ½ diopter for distance. Visual fields were within normal limits.

Ear, nose, and throat examination was negative, and x-ray examination of the sinuses and orbits was normal. Blood, urine, and basal metabolic rate were normal.

A preoperative diagnosis of tumor of the left orbit was made. On March 27, 1947, a firm fibrosed tumor was removed through an incision in the outer aspect of the upper lid.

The gross specimen consisted of a small portion of tissue measuring 15 by 10 by 10 mm., which was irregularly ovoid in shape, white, and of moderately firm, tough consistency. The cut surface presented a somewhat trabeculated appearance, with pinkish-red tissue between the trabeculations.

On microscopic examination the bulk of the tissue was formed by small, dark-staining epithelial cells, variably cuboidal, spindly, polyhedral, or flat. In the more solid areas they resembled basal cells. They were arranged in cords distributed through dense connective tissue as laminated structures with reduplication of lamina. The elements resembled basal cells forming irregular small islands which contained lamina filled or partly filled with pink-staining hyaline material. The pink-staining material occurs as round masses filling or partly filling the lamina. Occasional mitoses were seen. Several nerves were surrounded and infiltrated by the atypical epithelial cells. Along one margin of the section were fragments of normal-appearing lacrimal gland.

A diagnosis of adenocarcinoma, cylindroma in type, of the lacrimal gland was made.

Postoperative x-ray therapy was not deemed useful because of its inefficacy in this type of tissue. The patient is to be observed for recurrence, in which case radical exenteration will be performed.

Summary

The neurilemmoma is a rare type of tumor which may appear at any age and is of progressive growth. The lymphosarcoma is a highly malignant type of tumor which is radiosensitive and may be treated with x-ray alone if the diagnosis is made before operation. Adenocarcinoma of the lacrimal gland is perhaps less rare than the other two types. It is also a malignant growth for which operation may not be completely successful and to which x-ray therapy is ineffective.

The authors gratefully acknowledge the cooperation and assistance of Dr. John B. Hazard of the Department of Pathology.

References

1. Reese, A. B.: Orbital tumors and their surgical treatment. Am. J. Ophth. **24**:386 (April); 497 (May) 1941.
2. Elschnig, A.: Operations for tumors of orbit. Surg., Gynec. & Obst. **45**:65-73 (July) 1927.
3. Rottino, A., and Kelly, A. S.: Specific nerve sheath tumor of orbit (neurilemmoma, neurinoma); report of case with review of literature. Arch. Ophth. **26**:478-488 (Sept.) 1941.
4. Dandy, W. E.: Orbital Tumors: Results Following the Transcranial Operative Attack. (New York: G. E. Stechert and Company, 1942).
5. Iles, A. E., and Short, A. R.: Orbital tumors. Brit. J. Surg. **31**:147-150 (Oct.) 1943.

CARCINOMA OF THE THYROID GLAND APPARENTLY IN STRUMA FIBROSA (RIEDEL)

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THE differential diagnosis between Riedel's struma and carcinoma of the thyroid gland is often difficult because of their common features of mass, pressure, and infiltration of structures adjoining the thyroid gland. The occurrence of the combined lesion is a rarity despite the fact that adenomas are not uncommon in struma fibrosa. A case was recently encountered which presented clinical features consistent with either diagnosis and the unusual pathologic findings of a sclerosing lesion of the thyroid gland and an undifferentiated carcinoma.

Case Report

A married white woman, aged 38, was first admitted to the Cleveland Clinic on August 13, 1930, complaining of enlargement of the neck. She had first noticed slight enlargement seven years previously, and six years before admission a nodular enlargement of the thyroid gland, greater on the left, had been noted by her physician. The enlargement was described as the size of a goose egg. The thyroid mass was believed to resemble carcinoma, and removal was advised. However, operation was not performed, and the mass gradually increased in size. There had been no nervousness, palpitation, or tenderness.

Temperature was 98.2 F., pulse rate 72, blood pressure 110 systolic, 80 diastolic. Physical examination revealed the left lobe of the thyroid gland to be enlarged, firm, nodular, and freely movable. Otherwise the physical examination did not reveal abnormalities. The red cell count was 4,400,000, hemoglobin 80 per cent, white cell count 6700.

The diagnosis was adenomatous goiter without hyperthyroidism. Thyroidectomy was advised but was not performed.

The patient next returned on May 17, 1947. In 1931 she had had a right salpingo-oophorectomy for a twisted ovarian cyst and in 1933 dermatitis venenata due to mercolized wax. She had moved from Ohio to New York, and, while there, the goiter had disappeared.

About four months before entry the swelling returned. There was no local soreness, but the patient occasionally experienced some pain behind the left ear. There had been no difficulty in breathing or swallowing, no nervousness, and her appetite had been good. The skin on the arms and legs had become very dry during the preceding one and a half years. She tolerated hot weather better than cold.

The temperature was 98.6 F., pulse rate 76, respirations 20, blood pressure 150 systolic, 90 diastolic. Weight was 133 pounds, her normal weight being 137 pounds. The left lobe of the thyroid gland was stony hard, fixed, and enlarged about four times normal size. The gland moved slightly with swallowing.

Hemoglobin was 13 Gm. per cent and the white cell count 3900. Blood Wassermann and Kahn reactions were negative.

Roentgenologic examination of the chest revealed normal lungs. The trachea was deviated to the right and compressed along the anterior margin by an enlarged left lobe of the thyroid gland. On the oblique film there was a small area suggesting calcification in

the region of the left lobe. The diagnosis was carcinoma of the thyroid gland; Riedel's struma could not be entirely excluded.

A left lobectomy was performed on May 19, 1947, after biopsy and microscopic examination. The left lobe was stony hard, seemed to be fibrous, and the muscular capsule adhered to it.

Pathologic Examination

The gross specimen was 25 by 12 by 10 mm. and composed of firm, tough, opaque, yellowish-pink tissue, in part covered by tissue tags. Diagnosis was malignant tumor, possibly fibrosarcoma; Riedel's struma could not be ruled out.

The second specimen consisted of a thyroid lobe of roughly ovoid shape, 65 by 50 by 45 mm., weighing 97 Gm., accompanied by several flat portions of firm, tough, white tissue. The surface was pinkish-yellow with numerous tags of tissue attached over one area. Section revealed an eccentric ovoid grayish area, 45 mm. in diameter, surrounded by a white area 5 to 20 mm. in thickness. The latter zone was made up of tough, white, very firm tissue with

FIG. 1. Sectioned thyroid lobe, showing the somewhat circumscribed bulging area of undifferentiated carcinoma, and peripheral, dense, sclerotic zone.

a finely grained and, in part, laminated appearance. The central ovoid area was formed by soft, gray to purplish-gray tissue, with a slightly bulging surface and a fish-flesh appearance. There was one large zone of yellowish color, apparently necrotic. Several hard patches were present. (Fig. 1)

On microscopic examination sections from the rounded central zone revealed atypical epithelial cells in variable arrangement and of greatly varying type; irregular sheet-like masses with cells of rather large size and with occasional giant nuclei; scirrhous zones with sparsely distributed single small islands and cords of medium-sized atypical epithelial cells; trabeculations of spindly and polyhedral epithelial cells separated by blood-filled sinuses, and occasional patches of hyaline fibrosis. There were frequent mitoses. Broad zones of necrosis and calcification were present in some sections. A well retained fibrous capsule adjoined the neoplasm in areas. Two veins in the capsule of one section were partly filled with tumor.

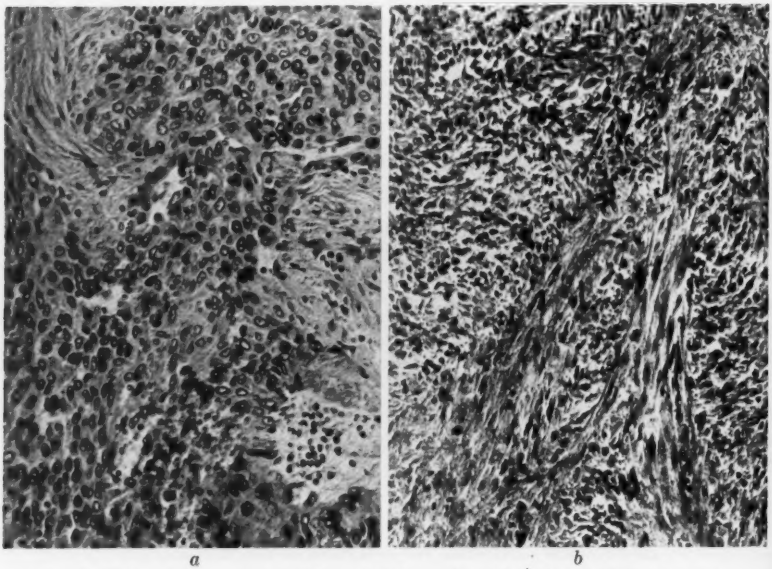
The broad peripheral sclerotic zone was formed in large part by dense, often hyaline, fibrous tissue containing scattered small acinar structures, some of which contained colloid and were formed by flat or cuboidal epithelium. Occasional giant cells of foreign body type

were present. There were other areas of greater cellularity blending with the above zones and resembling cellular fibrous tissue. Several blood vessels showed rather marked fibrous thickening of their walls. There were frequent foci and patches of lymphocytes, plasma cells, and some polymorphonuclears. Sections through the periphery showed infiltration of muscle by spindle cells and dense collagenous tissue. Rare cells in some sections presented irregular atypical nuclei. In phosphotungstic acid hematoxylin preparations, fibroglia were demonstrated in most of the units of the cellular spindle cell patches.

The pathologic diagnosis was undifferentiated carcinoma, medullary and spindle cell types, in Riedel's struma. (Figs. 2 and 3)

Following operation, radiation therapy was given. After 2400 r the patient showed such a severe reaction to therapy that treatment was terminated.

The patient was admitted to the hospital on October 8, 1947, because of paralysis of



a *b*

FIG. 2. Photomicrograph of undifferentiated neoplasm (x150). (a) Medullary type. (b) Spindle cell type.

the lower extremities. The thyroid was stony hard and three times normal size. Roentgenologic examination of the chest revealed multiple nodular shadows, which were interpreted as metastases. No lesions were demonstrated elsewhere.

Discussion

In order to explain the extensive fibrosis, two pathologic diagnoses were considered, diffuse scirrhous carcinoma alone or carcinoma arising in Riedel's struma. Over large areas in the peripheral zone, the sclerosed thyroid gland with remnants of atrophic follicles and patches of lymphocyte and plasma cell infiltration presented an histologic picture typical of Riedel's struma. In the cellular spindle cell foci in the thyroid tissue and peripherally the majority

of cells were identified as fibroblasts in the phosphotungstic acid hematoxylin preparations. In some sections, however, there were rare cells with atypical nuclei and without demonstrable fibroglia. The more central lesion was typically carcinomatous, with medullary masses of poorly differentiated cells and vascular spindle cell areas. The calcification was interpreted as probably resulting from a precedent adenoma. In some sections the cellular zones at the periphery were of neoplastic appearance, yet they were predominantly of fibroblastic composition, in immediate association with dense sclerotic patches and with foci of infiltration by lymphocytes and plasma cells. Though the histologic picture in the peripheral zone coincides with that found in Riedel's

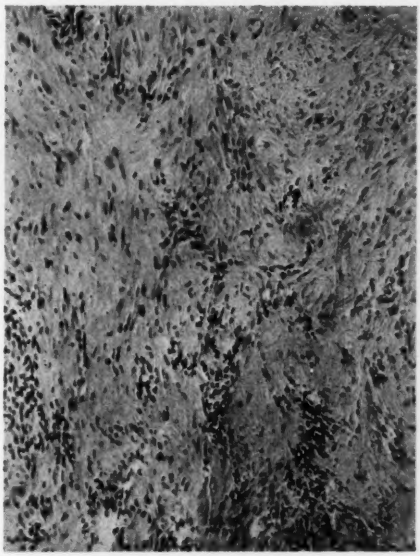


FIG. 3. Photomicrograph of peripheral sclerotic zone, showing dense collagenous connective tissue with atrophic thyroid follicles and patchy infiltration, principally by lymphocytes and plasma cells (x70).

struma, it is difficult to prove absolutely that this lesion was pre-existent, since an infiltrating desmoplastic tumor might itself produce such fibrosis. In our experience, however, an infiltrating neoplasm with such a sparsity of neoplastic units and such an abundance of dense hyaline stroma has not been encountered in the thyroid.

The occurrence of carcinoma arising in Riedel's struma is an expected possibility, considering that a fair percentage, variously estimated from 60 to 90 per cent, of adenocarcinomas of the thyroid gland originate in adenomas and the fact that adenomas are not uncommonly found in struma fibrosa. In a recent review at the Cleveland Clinic nine of fifteen specimens of the latter

lesion contained adenomas, and Eisen[1] reports four of seven instances. However, the rarity of Riedel's struma and the relative rarity of thyroid carcinoma offer an explanation for the lack of coincidence of the lesions. There is also a difficulty in establishing the presence of other lesions in a gland that is the seat of extensive carcinoma; the landmarks of preceding disease may be obliterated by the malignant lesion. Whatever the particular circumstances, a partial but rather extensive search of the literature has failed to reveal a reported case of the combined lesion.

This case illustrates several interesting clinical features. The presence of calcification or suspected calcification does not exclude carcinoma, although calcium is not commonly demonstrated in malignant neoplasms of the thyroid. Pain due to enlargement of the thyroid gland in both Riedel's struma and carcinoma is often referred to the ear or neck on the side of involvement. The neoplasm encountered in this case belongs to the most malignant group of thyroid carcinomas, being histologically atypical and showing readily demonstrable invasion of veins. The spindle cell variants of undifferentiated carcinoma of the thyroid gland frequently show rapid recurrence. This is well illustrated in an unusual case reported by Wikle and Ritzman[2] in which a massive local recurrence was found within four months of the primary excision and by this case, which showed recurrence and metastasis within five months. Radioresistance is a common feature of this type of undifferentiated thyroid neoplasm.

References

1. Eisen, D.: Riedel's struma. Am. J. M. Sc. **192**:673-688 (Nov.) 1936.

2. Wikle, H. T., and Ritzman, A. J.: Course of carcinoma of thyroid gland; report of unusual case. Am. J. Surg. **56**:507-512 (May) 1942.

Cleveland Clinic News

APPOINTMENT

Dr. William L. Proudfit has been made a member of the staff of the Section on Cardiovascular Diseases in the Division of Internal Medicine. Dr. Proudfit graduated from Washington and Jefferson College in 1935 and Harvard Medical School in 1939. He served in the U. S. Army Air Force from 1943 to 1946.

Dr. Proudfit is a member of the Academy of Medicine of Cleveland, the Ohio State Medical Society, and a Fellow of the American Medical Association. He is also an Associate of the American College of Physicians and a member of the Cleveland and American Heart Associations. He was certified by the American Board of Internal Medicine in 1946 and is the author of a number of papers in the medical literature.

BUNTS LECTURES

The Frank E. Bunts Educational Institute has scheduled the following Bunts lecture on April 14. This lecture will be held in the Founders and Staff Room of the Cleveland Clinic at 8 p.m. Visitors are cordially invited.

April 14, 1948—Dr. Paul Klemperer

Changes of the Collagenous Tissues in Disease

MEETINGS

Staff meetings are held on the first and third Mondays of the month, except from the middle of June to the middle of September, in the Founders and Staff Room of the Cleveland Clinic building at 8 p.m. All physicians are welcome to attend. In addition, a medical conference is held on Wednesday morning from 8 to 9 a.m. on the eighth floor of the Cleveland Clinic Foundation Hospital, a surgical conference on Thursday from 1 to 2 p.m. in the same place, and an x-ray conference Friday afternoon from 5 to 6 p.m. in the Founders and Staff Room of the Cleveland Clinic building except in the summer months. All of these conferences are also open to physicians who wish to visit them.